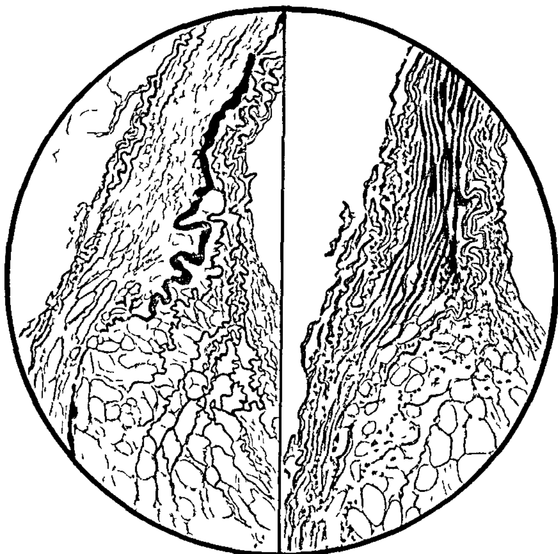


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THE PATHOGENESIS OF CORONARY OCCLUSION

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FOREWORD

A QUESTION which used to puzzle me in arterial pathology was how diseased arteries became narrowed Arteries are elastic tubes carrying a high internal pressure which is constantly pulsating and we would expect them to give way and dilate when diseased but in atherosclerosis and certain other lesions we sometimes find them narrowed almost to the point of occlusion This was not a problem which seemed to exercise other pathologists to any great extent since most of them accepted the orthodox teaching that narrowing was due to encroachment on the lumen of the artery either by degenerative swellings or by overgrowths of the intimal connective tissue as the histological picture seemed to show Nevertheless when arterial function was considered it was difficult to take the picture quite at its face value It did not seem likely that a degeneration or growth of young connective tissue could overcome the force of the blood pressure and actually close the arteries against it and so there remained the suspicion that some other process was involved

A possible solution suggested itself some years ago in the course of a demonstration of the principles of organization and canalization of arterial thrombi In this one saw how a thrombus could reduce the lumen of an artery and if organized look for all the world like an atherosclerotic thickening Thus was born the thrombosis hypothesis and from its birth to its histological confirmation was an unexpectedly short step The first few examples of severe coronary disease when examined with the hypothesis in mind seemed entirely to confirm it Moreover from a study of these and other arterial lesions in which narrowing was a feature a new principle seemed to emerge to the effect that when solid matter is deposited in the lumen of an artery it becomes covered with endothelium so that it is incorporated in the intima and forms a thickening of the vessel wall

This principle has now been confirmed in one way or another by a number of observers but it has been left to Dr Morgan to undertake a critical and independent examination of it from the point of view of coronary disease In the following monograph he has provided a comprehensive and I think in many ways decisive study On the subject of thrombosis he has put into words many of the views I myself would like to have stated and he has brought out other features – for example the relationship of intimal haemorrhage to fatty change – which are sometimes forgotten when etiology is considered Above all he has given a glimpse of what can still be done in the field of human morbid histology how old problems when examined from a fresh viewpoint can yield information which is both new and revolutionary Coronary atherosclerosis we may be sure is not the only such problem calling for histological reassessment and it is to be hoped that others will follow Dr Morgan s example I personally am much indebted to him

Newcastle upon Tyne August 1956 JOHN B DUGUID

To my wife

PREFACE

This book is based on material used for an M D thesis submitted to the University of Aberdeen in 1955 the main burden of which was to offer corroborative evidence for Professor Duguid s thrombogenic theory of coronary occlusion It is therefore neither a primer nor a manual and the sole reason for its presentation in book form is that condensation to a length appropriate to medical journals would reduce the argument to a series of dogmatic statements unsupported by evidence

This evidence is contained in the second half of the book and is largely expressed in terms of morbid histology as detailed and as fully illustrated as modern taste permits since it is this aspect of the pathogenesis of coronary disease that has been (and still is) most keenly debated The earlier chapters are devoted to the relevant literature and are intended to provide not merely a historical background to the present status but an abbreviated review of the literature of recent advances in other aspects of the pathogenesis of the disease

It is a pleasure to express my indebtedness to the following the Governors of Westminster Hospital for defraying expenditure on materials and technical assistance Professor R J V Pulvertaft for his exhortations Mr H N Stafford lately H M Coroner for the Western District of London for kindly affording me access to Police records of the circumstances in which several cases of sudden death were taken ill to the Public Relations Department of British Railways and London Transport for statistical information to Dr Peter Hansell and the staff of the Department of Medical Photography Westminster Hospital for assistance with the illustrations to Mr M Cuthbert for painstaking work with the histology and to Miss D Beasleigh for secretarial help

A D M

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1

The Rising Incidence of Coronary Disease

THE annual number of deaths due to coronary occlusion shows no sign of decreasing Between the years 1949-52 the Registrar-General s figures* for fatal cases of coronary occlusion reveal that the total is rising sharply as compared say with all forms of malignant disease at all ages

TABLE A

	Coronary Disease		Malignant Disease	
	Male	Female	Male	Female
1949	29 30	17 6	42 196	41 008
195	38 997	2 432	45 4 9	4 13

In the course of four years deaths from coronary occlusion have increased by 30 per cent as compared with 5-0 *per cent in cases of malignant disease* Even allowing for the increase of population or the greater expectation of life during those years they do not adequately account for the increased frequency in diagnosis of a condition that has been recognized by the medical profession for over a century and has been widely and energetically studied during the last 25 years

Confirmation by autopsy was doubtless lacking in a substantial proportion, and the Coroner s pathologist may consider that a number of the sudden deaths diagnosed by the practitioner on clinical grounds alone may have been examples of rupture of the aorta high dissecting aneurysm aortic incompetence spontaneous pulmonary embolism or heart block but when allowance has been made for these relatively uncommon conditions it is still clear that the figures given above reflect fairly accurately the depressing frequency of coronary disease

The pathologist is liable to see more of coronary disease than his clinical colleagues especially in individuals who die suddenly during their first serious attack Thus at Westminster Hospital during a 20-year period (1934-53) 377 autopsies were performed on cases dying of coronary occlusion Of these 51 were sudden deaths – i e in persons going about their daily duties or walking in the street who were suddenly taken ill and died at once or in the course of a few minutes The great majority of these died before they reached hospital the remainder in the Casualty Department One hundred and twenty-six were patients admitted to hospital with a previous history of coronary insufficiency o a known myocardial infarction or who had survived their first attack long enough to be diagnosed, clinically or by electrocardiogram Three hundred and thirteen

* *The Registrar General's Statistical Review (England and Wales) for the Year 1953* Table 7 International List nos. 140-05 and 4 0 H.M. Stationery Office London 1954

were males 64 females 71 per cent of the males were brought in dead as against 44 per cent of the females At the beginning of this 20-year period deaths from coronary disease constituted 1 3 per cent of the total number of autopsies performed this figure steadily increased to 7 7 per cent in 1953

The greater frequency of sudden death in males may in part be due to the geographical situation of Westminster Hospital in the heart of a metropolis where stress and strain are the rule and within a short distance of Victoria Station through which more than 150 000 people of all ages pass daily As will be shown later however there are indications that there is little relationship between heart attacks and the *act* of running to catch a bus or train In fact the frequency and the sex incidence may derive from an itinerant and predominantly masculine multitude equivalent to the population of a large town being concentrated in and around Victoria twice daily

In view of the figures quoted it is remarkable that although the nature of atherosclerosis to which 95 per cent of the cases of coronary occlusion are still attributed (*Wartman and Hellerstein* 1948) has been debated for upwards of a hundred years opinion is still sharply divided as to the origin of this highly lethal disease The role of cholesterol metabolism was long regarded as fundamental in the evolution of atherosclerosis but in 1946 *Duguid* revived the teaching of *Rokitansky* by suggesting that the apparently atherosclerotic obstruction of coronary vessels could be more satisfactorily explained by interpreting the appearances as the late result of mural thrombosis The point is of considerable importance since adoption of the thrombogenic theory must inevitably modify the present approach to aetiology and treatment To set the argument in its context however it is necessary to dip into the literature of the past

Before doing so a word on the terminology adopted will be appropriate The concept of atheroma as a purely intimal lesion in the form of raised discrete plaques is valid when applied to a large vessel like the aorta In the coronary arteries the degree of thickening of the vessel wall is often severe enough to convert whole lengths of it into a rigid tube with calcified walls and an atrophic or partially absent media It is still arguable whether such a change is the result of lipid deposits or organized thrombosis and the term atherosclerosis is employed here to designate a hardening or thickening of the vessel wall in which the fibrous and lipid elements of atheroma are recognizable This is the sense in which *Marchand* introduced the term in 1904

To avoid circumlocution the unsuitable but convenient expression atheromatous abscess has been retained to designate a focus of fatty softening in an atherosclerotic plaque It is at least sanctioned by usage whereas more rational terms – e g atherocheuma (*Leary* 1936a) – have not been widely adopted

Early Observations on Coronary Sclerosis

CONSIDERING the universal and lethal nature of coronary occlusion its recognition by the medical world and the elucidation of its aetiology have been surprisingly tardy Thus *Harvey (1649)* despite the brilliance of his observations on the circulation of the blood failed to comprehend the nature of Sir Robert Darcy s chest pains and attributed the rupture of his left ventricle (almost certainly the result of myomalacia cordis) to 'an impediment to the passage of blood from the left ventricle into the arteries

In a valuable and scholarly review of the early literature of angina pectoris *Huchard* (1889) quotes illustrious sufferers such as Seneca and Louis XIV in whom however the evidence is wholly symptomatic This same author credits *Drelincourt* (1700) with the first observations on the pathology of coronary sclerosis

Three years later the Italian anatomist *Bellini* and the German *Thebesius* independently recorded observations on calcification of the coronary arteries Thus, Bellini *Vidimus nos lapidem adnatum ramis coronariis majoribus qua dextrum a sinistro ventriculo dirimunt* (We observed a stone next to the main coronary branches which separate the right from the left ventricle) and Thebesius *Ita Lipsiae videre contigit ramos majores arteriarum in corde humano per convexam superficiem ad cuspidem decurrentes hinc illinc ex parte osseos redditos et ex parte tantum membranaceos visse* (Thus at Leipzig one happened to see the main arterial branches to the human heart running over its surface towards the apex rendered bony in part here and there and in part membranous)

Early comments on the relation of coronary sclerosis to cardiac symptoms were made by *Senac* (1749) and *Morgagni* (1761) The former who was the consultant physician to Louis XV performed an autopsy on a certain friar who was subject to palpitations *Les arteres coronaires etoient ossifiees elles formoient des rameaux semblables a des branches de corail*

More detailed and certainly more celebrated is the extract from the *De Sedibus* of Morgagni in which he records the clinical history of a Venetian woman who had a history typical of angina pectoris and died in 1707 at the age of 42 *A concitatis corporis motibus ingruebat molestus quidam angor intra superiorem thoracis sinistram partem cum spirandi difficultate et sinistri brachii stupore quae omnia ubi motus illi cessarent facile remittebant* (A certain unpleasant pain in the left upper part of the chest accompanied by difficulty in breathing and numbness in the left arm became worse on violent bodily movements all of which readily subsided when these movements ceased)

An autopsy was performed *Universum truncum majoresque ramos aperuimus in illoque ab ipsa origine pone semilunares valvulas quae durae hic illic erant et cum futuri ossis initiis ad iliacas usque arterias descripta vitia animadvertimus* (We opened the whole

[aortic] trunk and its main branches and in that branch at its very origin behind the semilunar valves which were hardened here and there with early bone formation we observed the lesions described right up to the iliac arteries)

The term Angina pectoris was suggested by *Heberden* who described the symptoms in 1768 in a paper read to the College of Physicians He was uncertain whether the malady was seated in the sternum or more deeply and lamented the fact that the sudden death of his patients prevented his attending an autopsy on any of them In 1778 however *Jenner* wrote a letter to Heberden on the subject of their common friend John Hunter who had been having anginal attacks for several months Jenner offered his views on the pathology of the condition based on two recent autopsies

In the first of these I found no material disease of the heart except that the coronary artery appeared thickened As no notice had been taken of such a circumstance by anybody who had written on the subject I concluded that we must still seek for other causes as productive of the disease but about three weeks ago we found the same appearance of the coronary arteries as in the former case But what I had taken to be an ossification of the vessel itself Mr P * discovered to be a kind of firm fleshy tube formed within the vessel with a considerable quantity of ossific matter deposited irregularly through it

Jenner considered it possible that all the symptoms might arise from this one circumstance and concluded by asking Heberden s advice as to whether he should communicate the idea to Hunter in view of the latter s condition This historic letter was never posted and was found later among Jenner s papers He did however record his views in a second letter to *Parry* who reproduced it verbatim years later (1799) In this Jenner recalled that he saw his first fatal case of angina pectoris when he was 23 The autopsy was performed by Hunter in 1772 and subsequently published by Heberden but on that occasion wrote Jenner the coronary arteries were not examined The letter goes on to describe the two autopsies referred to above the writer adding that on the second occasion he had taken a wager with his colleagues that he would find the coronary arteries diseased

Jenner is thus the first British pathologist to have understood the relation between coronary sclerosis and angina pectoris He deferred publishing his conclusions out of consideration for his mentor John Hunter and those colleagues to whom he privately communicated his beliefs rejected them After Hunter s death in 1793 however Jenner had the satisfaction of receiving a letter from *Home* who had assisted at Hunter s autopsy freely admitting that the coronary arteries were considerably ossified and concluding with the remark this case is very much in favour of your theory

Some years after Heberden s account of Angina Pectoris *Fothergill* (1776) published full details of two fatal cases with autopsy reports In the first of these the heart revealed a small cicatrix near the apex but there is no mention of the coronary arteries The second autopsy was performed on March 14th 1775 by John Hunter who wrote 'The two coronary arteries from their origin to many of their ramifications upon the heart were become one piece of bone However he made no comment on this finding in relation to the symptoms nor did Fothergill in the discussion that followed and there is no written

* M Paytherus.



EDWARD JENNER (1749-1823)

Mezzotint by John Raphael Smith (1752-1812). From an impression in the Wellcome Historical Medical Museum



CARL VON ROKITANSKY (1804–78)
From the lithograph in the Wellcome Historical Medical Museum

evidence that Hunter ever surmised the nature of the pathology of the disease that was to kill him although he did describe in some detail his symptoms to his son-in-law Everard Home (*Home* 1794)

After his death however some misunderstanding arose on this score and in 1815 *Hodgson* wrote that Mr Hunter and *subsequently** Dr Jenner and Parry ascribed the symptoms of angina pectoris to the deposition of calcareous matter in the coronary arteries of the heart whereby the stream of blood destined for that organ is so much diminished that its substance degenerates and wastes its muscular power is lessened and ultimately is insufficient for the purposes of the circulation

But if Hunter ever did suggest such a theory by word of mouth it is odd that *Matthew Baillie* his nephew and pupil should make no mention of it in the second edition of his *Morbid Anatomy* published four years after his uncle s death yet in the third edition of 1807 he added a section on the relation of coronary ossification to angina pectoris referring the reader in a footnote to Jenner s letter to Parry published 8 years earlier

Hodgson goes on to observe that coronary sclerosis is not present in every case of angina which may also occur with cardiac or aortic aneurysm He has this to say on the aetiology of atherosclerosis in general The frequency of the deposition of calcareous matter in the arteries of subjects advanced in life has been a cause of much speculation and some have conceived that in such instances it ought not to be regarded as a disease but as the natural effect of protracted existence Were this however the case we should expect that its extent would be proportionate to the age of the subject which is by no means the fact for in the few recorded instances of longevity which have been accurately examined this condition of the blood-vessels was not very remarkable In a footnote he adds On the other hand calcareous matter is sometimes deposited in the arteries of very young subjects

* *My italics*

III

The German School of the Nineteenth Century

In the hundred years that followed the pathogenesis of coronary sclerosis was only one facet of the wider problem of atherosclerosis as the medical horizon came to be dominated by the great German school of morbid histology In view of recent publications the opinions of its founder *Rokitansky* are of particular interest today In his *Manual of Pathological Anatomy* (1841-46) he says of atherosclerosis It consists in an excessive formation and deposition of the lining membrane of the artery derived from the mass of the blood and at the same time constitutes hypertrophy of this membrane A fairly accurate account of the gross pathology follows including observations on its frequency at bifurcations or around the mouths of branch arteries There is a comment on the increased vascularity of the adventitia but as the series may have included syphilitic arteries this observation is of dubious value

In considering the aetiology he notes the importance of age dismisses inflammation and regards the adventitial reactions as secondary phenomena The deposit he states flatly is an endogenous product derived from the blood and for the most part from the fibrin of the arterial blood The underlying cause of the fibrinous deposit he regards as a particular type of blood-crasis

The deposition continuously increases in thickness by addition of new strata he continues Vascularization of the plaque from the lumen was known to him for he describes a system of fine canals in aortic plaques which convey blood from the lumen to the interior of the plaque but do not appear to link up with the adventitial vessels These canals are undoubtedly the result of partial resorption in the deposit very likely the same process which we have noticed in a fibrinous coagulum in the heart where it rendered the coagula porous and caused them to acquire a cavernous structure

The plaque then undergoes (1) an atheromatous process and (2) ossification In the former he describes pultaceous softening with fatty globules cholesterin crystals and calcium salts liable to rupture by the force of the blood a process apt to be followed by fibrinous vegetations on the surface The presence of blood or haemic pigments in a softened plaque is regarded as the result of penetration from the lumen

By ossification he means simple calcification which he adds may coexist with atheromatous softening a view not widely shared at that time Rokitansky had also observed that arteries are affected to an unequal degree the aorta being more frequently involved than the femoral artery the coronaries than the brachial artery while some vessels are barely affected at all

Rokitansky s main thesis of fibrinous deposition was criticized by *Virchow* (1856) and thereafter fell into disfavour Virchow distinguished carefully between fatty infiltration

(fatty usure) which he described as a degeneration of the connective tissue cells below the lining endothelium of unknown origin and atheroma which he regarded as a fatty change occurring in the deepest part of the intima and separated from the lumen by a layer of connective tissue As this fibrous layer was directly continuous with that of the healthy intima at the margins of the plaque he rejected Rokitansky s theory of a surface deposit presumably being unaware of the rate of regeneration of endothelium and elastic tissue

He added an interesting note on cholesterol (1858) We see in every case where fatty products remain stagnant for a considerable time within a closed cavity in which but little interchange of matter can go on that the fat sets free cholestearine He held that cholesterol-formation was a late manifestation of atheroma and professed ignorance as to whether it previously existed in combination with the fat or whether a new formation had occurred in the deposit Atheroma in Virchow s view was a chronic inflammatory disease of the intima (Endarteritis chronica deformans) At a later date he came to postulate a blood dyscrasia as the underlying cause His final views were elaborated by his pupil *Rindfleisch* (1867) who believed that mechanical factors play a part in determining the localization of the plaque on those parts of the vessel wall exposed to the full impact of the blood Other factors are age alcohol and loose living

Rindfleisch explained the sequence of events thus first there is an overgrowth of fibrous tissue of inflammatory origin Then since the intima is avascular thickening leads to malnutrition of the deeper layers followed by fatty degeneration atheromatous softening abscess-formation and ulceration

For the next 40 years Virchow s conception of atherosclerosis prevailed a conspicuous heretic being *Thoma* (1883) who believed that the intimal changes were secondary to disease of the media Weakening of the vessel wall by pressure of the blood he argued causes the media to bulge outwards with the formation of shallow pouches In the course of a few months these are filled up by connective tissue thickening of the intima in order to restore the lumen to its normal size and shape The disease is progressive however and further stretching causes necrosis in the plaque with swelling probably due to the absorption of fluid and the plaque comes to project into the lumen Atheromatous softening of the hyaline portions follows This unorthodox theory has been periodically revived (e g *Bork* 1926 *Crawford and Levene* 1953)

Meanwhile the effect of coronary occlusion on the myocardium had been studied by *Cruveilhier* (1852) who observed gangrene following calcareous infiltration of the mouths of the diseased vessels It is surprising in view of the injection experiments of Thebesius and Morgagni more than a century before that he should have considered the coronary arteries as incapable of affording a collateral circulation In 1880 *Weigert* advanced the view that sudden coronary occlusion causes myocardial infarction while gradual narrowing leads to replacement fibrosis

Marie (1896) showed that cardiac rupture cardiac aneurysm and certain forms of myocardial fibrosis are all the result of obliteration of the coronary lumen He insisted that atheroma alone even if severe or calcified is not enough to cause infarction and that

careful dissection will always reveal total occlusion of one of the main coronary branches He differed from Weigert on the evolution of myocardial fibrosis believing that if the collateral circulation is good the resultant fibrosis is patchy and massive if it is not but in either case the fibrosis is the result of necrosis following sudden occlusion of a large branch

The era of static microscopy ended with *Jores* (1898 1903) who emphasized the significance of hyperplasia of the elastic lamina in arterial disease Since the days of *Lobstein* (1833) who introduced the word arteriosclerosis had been regarded as a thickening of the arterial walls sometimes but not necessarily associated with atheroma or calcification Jores however proposed that its usage should be limited to intimal hyperplasia accompanied by proliferation of the musculo-elastic layer as distinct from atheroma which he regarded as a purely degenerative phenomenon characterized by fatty change

Klotz (1906) pointed out that after all arteriosclerosis was a clinical term too and there was a danger that clinician and pathologist might use the same word in a different sense What was worse people came to think of atheroma and arteriosclerosis as two quite different diseases (e g *Pitt* 1908) and this resulted in a muddled nomenclature for many years to come *Marchand* (1904) had suggested the hybrid atherosclerosis not so much to avoid this confusion as to emphasize the frequency with which hyperplastic and degenerative changes are found in the same vessel the term however has not met with universal acceptance

IV

Experimental Atherosclerosis

It was about this time that experimental atherosclerosis became a reality Early attempts to induce lesions by traumatizing the vessel in various ways had done little but cause intimal fibrosis probably post-thrombotic This work is briefly reviewed and dismissed by *Klotz* (1906)

In 1903 *Josué* by giving rabbits repeated injections of adrenalin obtained changes in the abdominal aorta resembling calcified atherosclerosis But a closer microscopic study convinced *Fischer* (1905) that they were essentially medial in origin first fatty then calcareous and that any intimal thickening was in the nature of a secondary and compensatory phenomenon Today these changes would be considered analogous to the sclerosis of Monckeberg

Klotz (1906) injected various strains of bacteria intravenously into rabbits and produced intimal lesions which *Saltykow* (1908) who repeated the experiments claimed to be very like those of human atherosclerosis – raised yellow plaques single or confluent throughout the aorta and particularly involving the mouths of the intercostal arteries Microscopically the intima and the inner layer of the media contained fine fat droplets later taken up by phagocytes The fatty accumulation was often covered over by a fibroblastic proliferation just below the endothelium lining the vessel Other changes were mucoid degeneration proliferation of fine elastic fibrils and on one occasion calcification

Saltykow regarded the fibrosis as inflammatory in origin and believed his experiments supported the theory of an infective origin in human atherosclerosis However in the following year *Ignatowski* (1909) produced comparable intimal lesions by feeding rabbits on a diet of milk meat-extract and egg-yolk The aortic plaques took some time to evolve and were accompanied if not preceded by cirrhotic changes in the liver a type of nephritis and hypertrophy of the adrenal glands Microscopically the characteristic intimal lesion was an accumulation of large cells with a foamy cytoplasm

As the protein intake of a rabbit is normally low Ignatowski attributed his results to protein intoxication They were confirmed by *Starokadomsky and Ssobolew* (1909) who failed at the same time to reproduce Saltykow s findings also by *Stukkey* (1910) and *Fahr* (1912) Stukkey by feeding rabbits on combinations of milk egg-white egg-yolk and meat extract was able to show that the aortic lesions were most severe in animals fed on an egg-yolk combination He later (1912) was able to produce similar lesions by feeding ox-brain to rabbits

Fahr suggested that Saltykow s results were due not to the bacterial agency but to the milk on which they were fed and for many years little more was heard of the infective theory of atherosclerosis *Chalatow* (1912) fed egg-yolk to rabbits and observed lipid

deposits in the liver and aortic intima which he suggested were largely cholesterol an observation which *Wesselkin* (1913) was able to confirm

The obvious inference now was that the rabbit lesions were due not to protein but to cholesterol which is in considerably greater concentration in egg-yolk than in the other proteinous foods administered Accordingly *Anitschkow and Chalatow* (1913) fed rabbits with cholesterol dissolved in sunflower seed oil over a long period and were able to reproduce consistently severe atheromatosis of the aorta and lipid infiltration of the liver spleen and adrenal glands each of which contained cholesterol

Microscopically the intima showed first of all fat droplets mostly anisotropic and with the thermal reactions of cholesterol These lay in the subendothelial ground substance and did not involve the lining endothelium Later on leucocytes and large foam-cells appeared the latter containing anisotropic lipid The variety of intermediate cell forms led the authors to conclude that the foam cells were storage cells derived from the lymphocytes and monocytes of the blood elaborated to deal with the excess of cholesterol infiltrating the intima from the blood-stream Subsequent breakdown of these cells led to an extra-cellular accumulation of lipid Mature lesions showed degeneration of the subjacent elastic lamella and the formation of a fine elastic network in the plaque Sometimes the underlying media also showed degenerative changes Finally fibrous thickening of the intima took place and as a result of damage to the elastic lamella dilatation of the whole vessel

This work is quoted in some detail because it was a distinct milestone in the study of atherosclerosis The normal rabbit diet is cholesterol-free and spontaneous atheroma is very rare in rabbits (*Steinbiss* 1913 *Nuzum et al* 1930) Still since all animal cells contain cholesterol the rabbit must be provided with some metabolic device for synthesizing it (*Schonheimer* 1931) The rabbit s metabolism appears to be incapable of dealing with large amounts in the diet and the entire reticulo-endothelial system becomes saturated (*Schonheimer* 1924) including the aortic intima through which the excess lipid infiltrates from the bloodstream causing atherosclerosis The animals all have hypercholesterolaemia though the degree of atheroma is not proportional to the dosage of cholesterol (*Wacker and Hueck* 1913) It has since been shown however that it is approximately parallel to the degree of hypercholesterolaemia (*Pollak* 1945) Finally while some other experimental animals – e g guinea-pigs – are susceptible to feeding experiments (*Anitschkow* 1922) others – e g white rats – are not presumably owing to a different type of cholesterol metabolism (*Anitschkow* 1913)

The significance of all this lies in the fact that by feeding cholesterol to animals unused to it lesions closely resembling human atherosclerosis can be produced the first stage of which appears to be a fatty *infiltration* and not a primary degeneration as had hitherto been supposed in the case of human lesions this being so the metabolic factor in human atherosclerosis acquired a new significance from that date

The seeds of this theory had already been sown It had been claimed by *Ribbert* (1904) that plasma containing lipid infiltrates the vessel wall and initiates atheromatous changes a view that must have influenced *Aschoff* who was present at the lecture as he later (1907)

wrote that the cholesterol in atheromatous plaques was derived from lipid infiltration from the circulating blood *Lemoine* (191-) had expounded the theory that the lipid deposits in human arteries are due to an excess of cholesterol in the blood and now Anitschkow s experiments gave a practical foundation to these concepts

The implications of this spate of experimental activity profoundly influenced the approach to the problem for the next 20 years Anitschkow s observations were repeatedly confirmed – e g by *Bailey* (1916) who gave the first account of cholesterol atherosclerosis in English Modifications of the feeding method narrowed the gap between experimental and human atherosclerosis *Schoff* (19-7) showed that by feeding cholesterol to rabbits for 7 months followed by 6 months of cholesterol-free diet the patches formerly rich in lipid became fibrous He also showed that dietary atherosclerosis in the rabbit s aorta could involve the mouths of coronary arteries *Anitschkow* (19-8) described in detail the regressive changes in the lesions of experimental animals fed over a period of 2-3 years

But although the similarity between human and experimental lesions seemed clearly established doubts remained about the pathogenesis *Aschoff* (1914) while admitting the validity of Anitschkow s results was unable to accept the idea that the process in man was simply an overloading with lipid and formulated a theory which involved an additional mechanical factor He held that functional wear and tear and overstretching of the elastic cause a loosening of the ground substance of the intima followed by reactive proliferation of elastic tissue but at the same time permitting lipid to permeate the intima The latter is taken up by phagocytes causing a cellular reaction Continued swelling of the ground substance and accumulation of lipid lead to a secondary degeneration with breakdown of foam cells and the formation of cholesterol esters Fatty acids are released which combine with calcium to form indurated plaques

Thus atherosclerosis (wrote Aschoff) is the result of diverse causes and the process may be accelerated by secondary factors such as diabetes or hypertension In the Lane Lecture (*Aschoff* 19-4) he went further and distinguished between the *atheromatosis* of youth an infiltrative change which he regarded as largely reversible and *atherosclerosis* in the second half of life with irreversible tissue changes produced by the secondary degenerative breakdown mentioned above *Duguid* (1926) suggested that the localization of lesions around the mouths of branch arteries was due to a shearing stress occasioned by overstretching the main vessel

At least one fairly obvious contributory factor was hypertension and *Anitschkow* himself (1914) now showed that fluctuations in the blood-pressure evoked by compression of the rabbit s abdominal aorta or by suspension by the legs or by injections of adrenalin when followed by cholesterol feeding would produce atherosclerosis earlier or with smaller amounts of lipid in the diet The feeding experiments of *Fahr ck* (1915) also suggested the presence of some toxic or mechanical factor

Ssolowjew (1932) by first traumatizing the carotid arteries of rabbits and then feeding cholesterol demonstrated that the injured intima was more prone to lipid infiltration than the adjacent healthy vascular lining The importance of local factors in determining the

tance foreign to its diet Other animals fail to respond only because their cholesterol metabolism is adequate

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wrote that the cholesterol in atheromatous plaques was derived from lipid infiltration from the circulating blood *Lemoine* (1912) had expounded the theory that the lipid deposits in human arteries are due to an excess of cholesterol in the blood and now Anitschkow s experiments gave a practical foundation to these concepts

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site of the lesions was also demonstrated by *Harrison* (1933) who administered irradiated ergosterol to rabbits in order to produce a patchy calcification of the media and then fed cholesterol to evoke atherosclerotic plaques The two lesions occurred independently and were situated alternately in the vessel s circumference without overlapping By reversing the order of the experiment he produced the same result As both types of lesion reduced the mobility of the vessel wall he concluded that disorderly movement was a factor in their localization

In a later experiment involving lumbar sympathectomy to cause persistent arterial dilatation in one hind limb *Harrison* (1939) found that cholesterol feeding caused more extensive lesions on the affected side He considered that this result lent some support to Thoma s theory that atherosclerosis is secondary to a weakness of the underlying media

A minority rejected the role of cholesterol even in experimental atherosclerosis e g *Newburgh and Clarkson* (1923 1926*) who argued that Saltykow s rabbits had been fed on milk which has a low cholesterol content but is rich in protein nevertheless the lesions that followed contained as much cholesterol as those of Anitschkow s experiments In their own experiments Newburgh and Clarkson produced hypercholesterolaemia and aortic lesions in rabbits by feeding lean meat with a cholesterol equivalent of only one-tenth of that required to produce atheroma by feeding cholesterol alone The hypercholesterolaemia they attributed to a metabolic disturbance evoked by the toxic influence of a high protein diet

The infective theory too was revived by *Benson et al* (1931) Noting that septicaemia in the young may be accompanied by fatty infiltration of the aorta and that streptococcus viridans had been recently recovered from the clots in certain fatal cases of coronary thrombosis they injected streptococci into rabbits and fed them with cholesterol This produced small intimal thickenings mostly fibrous whereas the control animals fed on cholesterol without bacterial injection showed nothing They therefore concluded that infection plays an important part in precipitating cholesterol on the inflamed walls of arteries *Jones and Rogers* (1934) also found streptococci in the walls of sclerotic coronary vessels and maintained that chronic sinusitis was a factor in the disease These views find little favour today

A champion of the cholesterol infiltration theory of human atherosclerosis was *Leary* (1934) who found the aortic plaques of young people identical with the experimental lesions in rabbits He formulated the theory that in youth the cholesterol is largely re-absorbed and replaced by fibrous tissue but that the cholesterol metabolism of the aged is defective and the lipid accumulates to form atheromatous abscesses and ulcers — lesions by the way not observed in experimental atherosclerosis Later (1935a) he elaborated this theory stating that milk and eggs are foods intended for the embryonic or infant stage of *animal life and that prolonged ingestion of such substances leads to atheroma Man he* declared is the only animal that ingests eggs and milk during a lifetime Man is also the only animal that dies in early life from coronary sclerosis The inference intended to be drawn from this fallacious syllogism is obvious

* See Clarkson and Newburgh (19 6)

Leary's painstaking studies of youthful human lesions (1936a) led him to conclude that the first change is the appearance of fine neutral fat droplets in the ground-substance of the intima. These are taken up by *globular lipophages* situated near the surface in which cholesterol droplets are seen in ester form. These cells migrate by amoeboid action to the deeper layers where they disintegrate and deposit their contents. The cholesterol is then taken up again, this time in crystalline form, by phagocytic fibroblasts – branching amoeboid cells which Leary terms *fibrolipophages* – after which the lipid loses its anisotropism and disappears altogether. The fibrolipophages, which show no tendency to disintegrate like their globular equivalents, now revert to fibroblasts and form a loose reticular tissue. In old age globular lipophages only are seen, and the lipid tends to accumulate to form atheromatous abscesses with a minimal reticulin response.

In a later series of experiments on rabbits *Leary* (1941) modified these views. He was able to photograph foam cells apparently entering the aortic intima from the lumen. Since similar cells can be demonstrated in the animal's liver, adrenals and pulmonary capillaries, he suggested that the cholesterol, after being absorbed by the gut, is esterified in the liver and the excess stored in the Kupffer cells. These then migrate into the bloodstream and are conveyed to other organs including the aortic intima. These foam cells, besides being amoeboid, are tissue irritants and cause fibrosis in the liver as well as in the aortic plaques.

The theory that the foam cells are conveyed to the plaque by the bloodstream has suffered a reverse following the observation of *McMillan and Duff* (1948) that mitotic figures are not uncommon in pure foam-cell lesions, strongly suggesting that most, if not all, of these cells arise *in situ*. However, their irritant effect is supported by the work of *Christianson* (1939) who showed that if various fatty substances are injected into the femoral arteries of dogs, most of the injected material is rapidly absorbed, but the cholesterol tends to remain and to provoke a fibrous reaction. *Leary* (1944) believes that after the foam cells have disintegrated the fibroblasts come to contain an excess of fatty acids in which the cholesterol is dissolved. The lipid then disappears from these cells, which return to normal leaving only a fibrous thickening. In this way regression of the atheromatous lesions may occur.

In a notable survey *Duff* (1935) critically examined the relation of experimental atheroma to human lesions. Among other things he stressed that (1) the experimental lesions are produced by feeding a substance not ordinarily in the rabbit's diet, and in an animal not normally susceptible to atherosclerosis; (2) age is not a factor in the rabbit lesions; (3) only certain experimental animals will develop the disease; (4) hypercholesterolaemia and cholesterosis of certain viscera are constant and necessary conditions for the development of vascular lesions. He therefore concluded that while cholesterol might be a factor in human atherosclerosis there must be some additional element, probably traumatic, which determines the localization of the lesions.

Leary (1936b) replied that the absence of spontaneous atherosclerosis in the rabbit made it an ideal experimental animal, and that the saturation of its blood and reticulo-endothelial system following cholesterol feeding were simply due to defective metabolism of a sub-

stance foreign to its diet Other animals fail to respond only because their cholesterol metabolism is adequate

In any case few will deny that the cholesterol feeding experiments have given a tremendous impetus to research on atherosclerosis and the method is still widely used in the assessment of contributory factors One drawback has been the time taken in the evolution of the lesions but in recent years *Bevans et al* (1948) have shown that intravenous injections of colloidal cholesterol will produce quicker results with less lipid indeed *Pollak* (1953a) thinks the resulting lesions are more like human plaques than those induced by the feeding technique

V

Fatty Streaking and Atherosclerosis

THIS is a convenient occasion to discuss the relation of the fatty streaks that are commonly found in the aortic intima of quite young subjects lying immediately below the lining endothelium *Virchow* (1856) had regarded them as a degenerative process of unknown origin differing from the more deeply placed fatty accumulations of atheroma which he believed to be post inflammatory *Jores* (1903) observed an accompanying connective tissue proliferation and was the first to believe the process to be merely an early stage of atherosclerosis *Aslanazy* (1907) agreed but thought the early streaking was a reversible process capable of complete regression in mild cases

Klotz and Manning (1911) observed that fatty streaking is common in young subjects suffering from acute infections The process starts with oedema of the subendothelial connective tissue and musculo-elastic layer followed by the appearance of spindle-shaped cells containing fat droplets some of which are anisotropic Fibrous thickening of the subendothelial layer follows and although the fat may be eventually absorbed a certain amount of fibrosis always remains

Klotz (1915a and b) later modified this view and came to believe that in toxaemia a reversible fatty degeneration can occur within the cells of the intima without involving the elastica He therefore restricted the definition of atheroma to the stage when the cells break down and the fat comes to lie free in the tissue spaces

Aschoff (1924) took much the same view but *Duguid* (1926) denying that the fatty change was primarily degenerative and intracellular as Klotz believed asserted that the process was one of lipid infiltration from the plasma into a damaged intima followed by phagocytosis and fibrosis so injuring the intima further and initiating a vicious cycle that resulted in atherosclerosis The majority of observers thereafter come to regard fatty streaking as an early form of atherosclerosis (*Zinserling* 1925 *Wolkoff* 1929) *Ssolowjew* (1931) found lipid droplets in the intima and inner media of the aortas of suckling rabbits a phenomenon not observed in older animals he therefore concluded that the maternal milk rich in cholesterol could initiate fatty streaking in young animals without invoking the agency of infection or toxaemia

Leary (1935a) neatly adapted the phenomenon to fit his own theory stating that the process was not completely reversible producing a mild residual fibrosis in younger subjects and gross atheromatosis in the aged Recently *Golberg and Morantz* (1955) have been able to produce an infiltration of chicken aortas *in vitro* remarkably like their human counterpart by injecting solutions containing cholesterol under pressure into the lumen of the vessel This was even successful in evoking a phagocytic response

VI

Atherosclerosis and Coronary Thrombosis

It is difficult for the pathologist of today to realize that the interest and enthusiasm aroused by the work of Anitschkow and his colleagues was not because of any light it might shed on the problem of coronary thrombosis the simple truth being that in 1913 this ailment was not a subject of widespread concern Though the relation of coronary thrombosis to underlying atherosclerosis had been observed by *Weigert Marie* and others many years earlier the prevalence of the condition and its occurrence in the absence of visible myocardial infarction were facts not universally appreciated Thus the observation by *Brooks* (1906) that coronary atherosclerosis was present in 270 out of 400 consecutive autopsies and more than twice as frequent as any other form of visceral atherosclerosis was largely of academic interest

Osler (1910) had noticed an increase in fatal cases of angina pectoris which had risen to 28 per million in England (the present death rate from coronary disease is something like 1200 per million) but he made no distinction between the symptoms of angina pectoris and coronary thrombosis Indeed not long before Osler s Lumleian Lectures *Sir William Broadbent* had said (1906) that there are no characteristic signs or symptoms by which thrombosis of the coronary arteries can be diagnosed

Herrick (1912) was among the first to realize that coronary thrombosis could give rise to symptoms differing from the angina of effort and *Allbutt* (1915) concurred even going so far as to assert that angina was not related to coronary occlusion Some manifestations of coronary disease remained unrecognized particularly in the form of sudden death and acute coronary occlusion without previous symptoms was considered quite unusual (*Willius* 1925)

According to *Rolleston* (1933) the prevalence of coronary thrombosis was not widely accepted in England until about 1926 and *Wearn* (1923) had written Coronary thrombosis with infarction of the heart as a clinical entity is a condition which is generally classed among the rarities of medicine Indeed it is considered so rare and of so little importance that most of the textbooks of medicine fail to give it mention or perhaps dismiss it with a brief paragraph while several of the larger systems of medicine ignore it altogether At best it is looked on as a terminal event impossible to diagnose and therefore of little clinical import The literature on the subject moreover consists for the most part of a very small number of case reports no attempt has been made to study a large series of cases confirmed by necropsy so that a clinical picture might be constructed which would enable one to recognize the condition It is little wonder then that the diagnosis is generally left for the pathologist to make

As a matter of fact the condition is not a very rare one it merely goes unrecognized

during life To account for this failure of recognition in part at least one needs only to consider the mode of death of the individuals who die from this cause As a rule death is sudden or follows a brief acute illness so that many of the patients are never seen by a physician at all or are only examined after death by a coroner If I have laboured this point it is to emphasize the background against which the alarming statistical increase in ischaemic heart disease began to be noticed

In the late twenties the familiar clinico-pathological syndrome rapidly took form *Levine and Brown* (1929) reviewing 145 cases found the disease commoner in males than females (7 2) with an average age of 57 8 and particularly affecting the anterior descending branch of the left coronary artery Hypertension was the commonest single associated feature In 44 instances of myocardial infarction 23 vessels were occluded by a definite thrombus while 12 showed severe narrowing without thrombosis For the latter group *De Coursey* (1934) suggested that the term *coronary occlusion* was preferable This was particularly applicable to cases Brought in Dead a considerable percentage of whom showed this condition (*Bedford* 1933)

Most were agreed that the left coronary artery is affected much more frequently than the right (*Wearn* 1923 *Faulkner et al* 1924 *Wolff and White* 1926 *Parkinson and Bedford* 1928 *Wolkoff* 1929 *Levine and Brown* 1929 *De Coursey* 1934 *Saphir et al* 1935 etc) Others have dissented (*Barnes and Ball* 1932 *Master et al* 1937a *Horn and Finkelstein* 1940) It was further noted that the most severely affected segments of the vessel lie outside the myocardium especially the first few centimetres of the main branches (*Levine and Brown* 1929 *Leary* 1934 *Saphir et al* 1935)

There was practically universal agreement about the correlation of coronary thrombosis and underlying vascular disease (*Wearn* 1923 *Willius* 1925 *Levine and Brown* 1929 *Wolkoff* 1929 *Saphir et al* 1935 etc) and statements to the contrary (e g *Libman* 1925) were unsupported by evidence *Hamman* (1926) allowed that occlusion was on occasion due to embolism but summarized the common pathological experience thus The chief cause of occlusion is arteriosclerosis of the coronary arteries and the final closure is due to thrombosis Thrombosis never happens in a healthy vessel By the most recent estimate 95 per cent of cases of coronary occlusion are attributable to atherosclerosis (*Wartman and Hellerstein* 1948)

VII

The Morphology of Coronary Occlusion

ATTENTION was therefore directed with renewed vigour to the morphology of the occluded segments No more than a brief chronological outline is given here most of the more detailed discussion being contained in the second part of this work in order to avoid irksome cross-reference

A pioneer in this field was *Leary* (1934) who thought that occlusion in the aged followed rupture of an atheromatous abscess and in the younger age groups infarction of a fibrous plaque occurred initiating thrombosis Below the line of attachment of the thrombi he observed a substance near the surface of the devitalized plaque with the tinctorial reactions of fibrin mingled with argyrophil fibrils from which he concluded that fibrinoid necrosis of the collagen had occurred due to infarction of the plaque

The same phenomenon had been previously observed by *Mallory* (1914) who regarded the substance as fibrin from the blood in view of its association with disintegrating red cells Following Leary s article *Clark et al* (1936) cut serial sections through a number of blocked arteries and noting the association of a fibrin-like substance with degenerate or ulcerated areas they concluded that it was fibrin deposited by blood infiltrating the diseased surface of the plaque from the lumen *Horn and Finkelstein* (1940) sought to explain the occasional absence of red cells in the fibrinoid material by suggesting that the latter was due to seepage of plasma into the weakened intima

Leary s theory of fibrinoid necrosis was revived by *Schlossman* (1942) who treated sections with trypsin before staining and showed that only a part of the material is dissolved As fibrin is digested by trypsin he concluded that the residuum must be degenerate collagen This however does not necessarily follow and the subsequent work of Duguid and others has done much to support the view that the substance in question is in fact fibrin

Considerable interest was aroused by the observations of *Paterson* (1936 1938) on the frequent association of intramural haemorrhage with coronary thrombosis Serial sections revealed that the overlying intima was often intact indicating that the bleeding had come from the capillaries of the thickened intima A significant clinical corollary (*Paterson* 1939a) was the plausible explanation it offered in cases of sudden death when the individual was at rest or asleep since a small intimal haemorrhage could well have initiated thrombosis some hours or even days previously Paterson excluded hypertension as a contributory factor in capillary rupture, since he observed the latter in the plaques of pulmonary arteries (1939b)

The arterial intima which in health derives its nutriment from the circulating blood in the lumen undergoes vascularization when thickened by atherosclerosis a fact that had

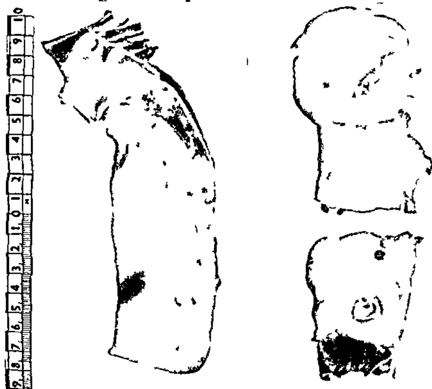


FIG 1

Gross ath osel rotic r ow g of two coron ry arte ır female aged 60 Aorta how only slight atherosel os s. Co p e with F g 2



FIG 2

Ext me therosel rosı of descend b tho c c ao ta ı f m le aged 92 The coron ry rteries howed omp r tively m ld atherosclero

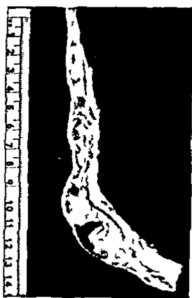


FIG 3

Arter o lerot a eury m of popl teal artery The content are soft a d y llow w th a high cholesterol content

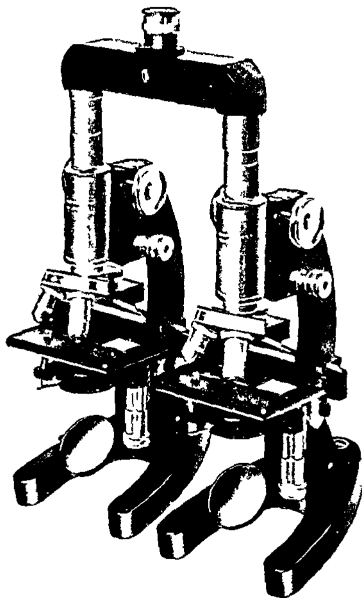


Fig 4
Microscopes w th comp rator eyep ece

hitherto attracted little attention although it had been noted by *Rokitansky* and stressed by *Raynaud* (1865) – by the latter as evidence of the inflammatory nature of atherosclerosis *Foster* (1876) had emphasized the role of hypertrophic vasa vasorum in arterial disease but erroneously assumed that they existed in the healthy intima as well *Wolkoff* (1929) had described a vascular network derived (*a*) from the hypertrophied vasa vasorum and (*b*) directly from the lumen developing after the deposition of cholesterol and concerned exclusively with its resorption *Leary* (1935a 1936a) whose principal observations had been on aortic plaques where vascularization is less conspicuous considered the vessels a late manifestation and insignificant in the evolution of the disease

Paterson however had not claimed that the capillaries played a part in the genesis of atherosclerosis he had merely emphasized their role in the subsequent coronary thrombosis a view endorsed by *Wartman* (1938) *Horn and Finkelstein* (1940) *Nelson* (1941) and others In the words of Horn and Finkelstein Once established the capillary network comes to form part of a vicious cycle through which the atherosclerotic process is advanced and may act as a decisive underlying factor in the subsequent occlusion of the main lumen

Winternitz et al (1938) had perceived the truth of this but had gone on to ascribe the whole of the atherosclerotic process to intimal haemorrhage a thesis which necessitated the existence of capillaries in the healthy intima in order to initiate the bleeding but an extensive review of the investigations into the blood supply of artery walls by *Ramsey* (1936-37) clearly reveals this view as untenable

It was by this time becoming apparent that the mechanism of coronary occlusion and the pathogenesis of atherosclerosis were problems which if not independent were at least separate a truth appreciated by *Levine and Brown* (1929) and glimpsed by *Marie* 40 years earlier each of whom had observed that severe coronary occlusion may be found along with a fairly healthy arterial tree elsewhere (Fig 1) For one thing the coronary arteries seemed to be more prone to occlusion than other vessels for another the occlusions were varied in type and often multiple

Koch and Kong (1932) believed that coronary occlusion (excluding syphilitic aortitis) took one of three forms (1) atheromatous softening raising the surface (2) fibrous proliferation (3) thrombosis *Saphir et al* (1935) saw no reason to distinguish (2) from organizing thrombosis *Leary* (1935b) in addition to the forms of occlusion quoted above thought that spasm might be a contributory factor *Paterson* (1936) thought thrombosis followed intimal haemorrhage and *Wartman* (1938) showed how an intimal haematoma may cause fatal compression of the lumen without necessarily rupturing into it

Von Albertini (1938) observed organizing thrombi in certain coronary segments related to zones of medial necrosis and perivascular lymphocytic infiltration of the adventitia He termed this condition chronic stenosing arteritis believing it to be a complication of focal sepsis and differing from true atherosclerosis

VIII

The Collateral Circulation of the Heart

BEFORE going on to more recent advances mention should be made of the researches into the coronary circulation as a whole During the nineteenth century opinion had differed on the existence of a collateral circulation some holding that the coronary arteries were end-arteries (*Cruveilhier* 1852 *Hyrtl* 1855 *Cohnheim* 1881) others the contrary (*West* 1882 *Marie* 1896) The evidence for the latter viewpoint is summarized below

(*a*) Clinico-pathological evidence – e g cases of complete and chronic closure of the mouth of a whole coronary artery without myocardial infarction (*West* 1882 *Galli* 1903 *Merkel* 1906)

(*b*) Injection of one coronary artery with a dye followed by its reappearance in the other vessel micro-examination revealing the dye in the smallest branches (*West* 1882)

(*c*) Experimental ligation of one or other division of the left coronary artery in dogs may be followed by complete recovery of the myocardium (*Miller and Matthews* 1909 *Smith* 1920) or by an infarct much smaller than the area supplied by the ligated vessel (*Smith* 1918)

Le Count (1918) claimed that injection techniques on post-mortem specimens were not a measure of the degree to which the vessels are *functionally* terminal – i e where occlusion of a branch may cause infarction without the collaterals being able to prevent it Further light was thrown on this subject by *Gross* (1921) in a major contribution which was based on injecting the coronary arteries of hearts of all age groups with a radio-opaque fluid and subjecting them to stereoscopic radiography He was able to show that the collateral circulation improves with advancing years suggesting that the aged are better able to withstand sudden coronary occlusion than middle-aged subjects

By injecting one coronary artery with mercury *Oberhelman and Le Count* (1924) demonstrated variations in the extent of the capillary bed of healthy hearts and argued that in some individuals the collateral circulation is adequate in the event of sudden coronary occlusion but in others it is adequate only if the occlusion occurs gradually Application of the Spalteholz technique (*Woodruff* 1926 *Robertson* 1930) revealed unsuspected anastomoses between the small arteries in the epicardial fat and the vasa vasorum of the aorta and still more were discovered by *Smetana* (1929) and *Hudson et al* (1932) All this helped to explain the survival of the myocardium in the presence of multiple occlusions (*Willius* 1925 *Master et al* 1937a)

Wearn (1928) recorded two remarkable cases in which the mouths of *both* coronary arteries were completely occluded by syphilitic aortitis although both vessels were of normal diameter 0 5 cm from their origin and there was no gross infarction Wearn s perfusion experiments on post-mortem hearts showed that 60–90 per cent of the coronary

flow escapes not into the coronary sinus but directly into the cardiac chambers through the Thebesian veins and he suggested these as a likely source of collateral circulation in the event of gradual coronary occlusion

It was eventually realized that coronary thrombosis is not only a recoverable incident but may be a recurrent phenomenon in the life of one individual *Parkinson and Bedford* (1928) and *Barnes and Ball* (193-) commented on the frequency of two or more infarcts in the same heart and *Saphir et al* (1935) by careful dissection of 34 hearts showing infarction were able to demonstrate 2 3 or 4 vascular occlusions in every case and concluded that at least 2 branches must be blocked before infarction occurs

A corollary of this work was the realization that the angina of effort coronary thrombosis and sudden death from coronary narrowing without thrombo is (generally attributed to ventricular fibrillation) might all have a common underlying pathology

Saphir and his co-workers also confirmed the ob ervation of *Parkinson and Bedford* (1927-29) that despite the fact of the right coronary artery being occluded in a substantial proportion of cases myocardial infarcts occurred in the overwhelming majority of instances in the distribution of the left artery – a curious phenomenon that has never been satisfactorily explained

White et al (1950) found that the average man after the age of 49 has a moderately severe degree of occlusion (grade 3 according to the classification detailed in Chapter XX) at some point in both right and left coronary arteries And *Schlesinger* (1940) stated that in 145 consecutive autopsies on males dying from a variety of causes 40 per cent of the hearts of men over 55 showed occlusions As most of these are less than 5 mm long more than half of them are liable to be overlooked in routine autopsy dissections (*Schlesinger and Zoll* 1941)

Coronary disease is most severe where the bulk of the blood supply to the heart comes from the left coronary artery intermediate where the right coronary artery predominates and least of all where the blood supply is evenly balanced between the two vessels (*Schlesinger* 1940)

IX

The Influence of Age and Stress

AGE

THE age factor in atherosclerosis – even of coronary atherosclerosis – had been a subject of speculation for over a century The remarks of *Hodgson* (1815) on this subject were noted earlier (p 9) Atherosclerotic arteries of different age groups were studied by *Aschoff* (1924) *Wolkoff* (1929) and *Leary* (1934) All were agreed that fatty streaking is more characteristic of youth and largely reversible while atheromatous abscesses are a feature of the older age groups *Zinserling* (1925) demonstrated fatty infiltration in the aortas of 6-month-old infants with the same localization as adult atherosclerosis Out of 302 aortas in children under 16 fatty streaking was present in 95 4 per cent

Gross et al (1934) *studied the coronary arteries of normal subjects from birth to old* age and observed hypertrophic changes in the intima shortly after birth with increased elastic and connective tissue In the second half of life they found all gradations to atherosclerosis and they therefore came to regard the whole process as the result of ageing However the accumulated traumata infections dietary indiscretions and metabolic upsets that constitute the so-called wear and tear of a lifetime are not to be regarded as strictly physiological since they may be avoidable or preventable thus while the observations of Gross and his colleagues on the vessels of different age groups are of considerable value their overall conclusion is not generally accepted

Some had noted an abnormal thickness in the coronary intima as compared with other arteries even at birth (*Ehrich et al* 1931 *Spalteholz and Hochrein* 1931 *Sappington et al* 1936 1941) and in 1946 *Dock* observed that this was more marked in male infants which he suggested might account for the apparent predilection of atherosclerosis for coronary arteries and the higher incidence in males He described connective tissue cushions on the intima which he regarded as an inherited peculiarity concerned with blood-flow however *Fangman and Helling* (1947) found lipid droplets and elastic fragmentation in these structures and preferred to consider them as an early manifestation of atherosclerosis

White et al (1950) recognized four degrees of coronary narrowing and were able to show that there is a rapid increase in the severity of coronary occlusion in males between the *ages of 30 and 49 reaching a maximum between 50 and 59 and thereafter falling off* slightly In women the degree of severity is less and the curve rises steadily nearing the male curve at about 70 (*Ackerman et al* 1950) There is thus a wide sex difference in the sixth decade (*Firstbrook* 1951)

STRESS

It may have been the mental association with the angina of effort that led to the belief

that stress was a precipitating factor in coronary thrombosis Doubtless another reason was the quite frequent occurrence of sudden death *during periods of overactivity* However in an early series by *Wolff and White* (1926) it was shown that some attacks occurred during sleep or at rest and *Luten* (1931) found no relation of coronary thrombosis to effort at all

Fitzhugh and Hamilton (1933) investigated the activities preceding attacks in 100 cases and found they usually followed some departure from the subject s normal habit of life – undue effort or fatigue travel emotional strain overeating alcohol or a surgical operation *Leary* (1935b) suggested that death during sleep might be due to coronary spasm occasioned by nightmares *Levy and Bruenn* (1936) pointed out that as the fatal thrombus is nearly always hours or days old it is rarely the *immediate* cause of death

The fullest correlation of coronary thrombosis with antecedent events was that of *Master et al* (1937a 1939a) They investigated many hundreds of cases and found that the disease occurred in all walks of life and all types of occupation Forty per cent occurred during sleep and there appeared to be no significant correlation with exertion emotion meals time of day or season of year Intramural haemorrhages were as common in bedridden patients as in physically active ones and was therefore probably fortuitous

Paterson (1939a) reasonably enough pointed out that if his theory of haemorrhage in the plaque initiating thrombosis hours or days before death was true then the patient s activity *at the time of* death was irrelevant Recent work by *Morris* suggests that the man of active physical habit is less prone to coronary disease than the more sedentary type As the approach is statistical it is treated in Chapter XVI

X

Cardiac Hypertrophy Electrocardiography

Two other points deserve mention The first is the myocardial hypertrophy which had been observed in association with coronary occlusion Some authors merely recorded the fact (*Faulkner et al* 1924 *Willius* 1925 *Levy and Bruenn* 1936) Others ascribed it to hypertension (*Barnes and Ball* 1932 *Bedford* 1933) and others to cardiac failure caused by multiple infarctions (*Master et al* 1937a)

But it is a demonstrable fact that in many cases of coronary occlusion the hypertrophy is not confined to the left ventricle and may occur in the absence of healed infarcts or gross interstitial fibrosis Thus *Davis and Blumgart* (1937) excluded cases of hypertension and cardiac failure but still found the average weight of the remaining hearts well above the normal controls (440 as against 275 grammes) Employing an established physiological principle they argued that chronic coronary insufficiency leads to overstretching of the undernourished myocardial fibres thereby stimulating the latter to hypertrophy From a recent large series *Yater et al* (1948) have reached the same conclusion

A second point only to be touched on since it lies outside the scope of the present work is the development of electrocardiography in ischaemic heart disease The experiments of *Smith* (1918 1920) who ligated branches of the coronary arteries in dogs have already been mentioned (Chapter VIII) They were accompanied by electrocardiographic studies and in due course similar aberrations were recorded in the graphs of human subjects notably inversion of the T-wave (*Smith* 1923) This afforded thereafter a valuable diagnostic aid especially in cases where the symptoms were equivocal or atypical

XI

Duguid's Thrombogenic Hypothesis

In the course of an excellent article on the morphology of coronary occlusion *Horn and Finkelstein* (1940) remarked The occurrence of parietal thrombi such as we have seen in this series and as others have observed also leads to confusion for when such a lesion is finally replaced by fibrous tissue and incorporated into the intima the affected segment of the wall appears exactly like an area which has been progressively thickened by fibrosis of a zone of intimal lipoidosis The implications of this observation however were not pursued

The thrombogenic theory of *Duguid* (1946) on the aetiology of coronary atherosclerosis was something of a bombshell On cutting deeper into the block of a recanalized thrombus he had been struck by the fact that it merged into what looked like a typical atherosclerotic plaque Serial sectioning of a number of narrowed coronary arteries (all admittedly of severe degree) strengthened his conviction that what is called coronary atherosclerosis is frequently the end-result of arterial thrombosis

Although he gave credit to *Rokitansky* for the original hypothesis it is necessary to realize that Duguid considerably elaborated the views of his prototype For example the concept of a clot at first completely or partially blocking the lumen and later shrinking to one side of the vessel to be overgrown by endothelium from the opposite side while the deeper part of the thrombus underwent fatty degeneration – such a sequence of events could never have been entertained a century ago It was in fact because he knew nothing of the rate of endothelial overgrowth of mural thrombi that Rokitansky s theory found red under the attacks of Virchow A host of discoveries were made in the next hundred years that served to make Duguid s hypothesis plausible – to name only one the collateral circulation of the heart

Besides mural thrombi Duguid noted that wisps of fibrin are often to be found adherent to the intima of the vessel or in varying stages of incorporation into the vessel wall by overgrowth of endothelium In this way it became possible to account for the buried streaks of fibrin that had puzzled others Indeed Duguid attached great importance to these believing them to be the essential link between thrombosis and atherosclerosis

These observations were later extended to atherosclerosis of the aorta (*Duguid* 1948) where he found similar minute incrustations on the intima of 19 out of 50 consecutive aortas of individuals whose ages ranged from 3 to 73 who had died from a variety of causes These fine wisps often too small to be seen with the naked eye could in the course of a lifetime account for substantial thickening In young children they were commonly found at the mouths of branch arteries associated with fatty streaking

Other observations elaborated the basic concept and offered new explanations of old

problems that had vexed earlier workers – e g disintegrating red cells were cited as a potential source of cholesterol superimposed layers of collagen separated by elastic membranes were seen to be the result of recurrent thrombosis the vessels in the plaque were the end-product of organized thrombosis (*Duguid* 1949)

Geiringer (1951a) re-examined occluded coronary segments in the light of this last suggestion and concluded that the superficial plexus described by *Wolkoff* (1929) was indeed the residue of organized thrombosis but he maintained like Wolkoff that the vasa vasorum also played a part in nutrition of the plaque If the superficial plexus is inadequate or absent the plaque is entirely dependent on the transmedial supply This however is capable of a strictly limited extension and if the plaque is more than 0 35 mm thick (or 0 5 mm in the aorta) the blood-supply is outstripped and the central layer of the plaque undergoes fatty degeneration It is fundamental to realize asserts Geiringer that intimal vascularization is a function of intimal thickness and not of atherosclerosis

Crawford and Levene (1952) modified this concept still further and advanced the view that endothelial cells derived from the endothelium lining the vessel (or rather overgrowing the clot) are capable of assuming the function of fibroblasts and organizing the superficial part of the thrombus without extensive capillary activity

Meanwhile *Harrison* (1948) had obtained confirmatory experimental evidence by injecting fragments of fibrin into the veins of rabbits and producing intimal thickenings in the pulmonary arteries by endothelial overgrowth of the emboli followed by fibroblastic proliferation at their base Anisotropic lipid droplets were found in one animal only probably because the fibrin did not contain red cells

Heard (1952) improved on these results by injecting larger autogenous fibrin clots into rabbits veins and showed that endothelial overgrowth was complete after 4 days reticulin began to appear after 5 days and collagen in 6 Granulation tissue had replaced the fibrin in a week and after a month only a fibrous thickening remained *McLetchie* (1952) by injecting rabbits with Russell viper venom produced two types of lesion (*a*) a thin layer of fibrin spread diffusely on the vessel wall which underwent organization accompanied by a proliferation of elastic tissue and (*b*) red mural thrombi which became organized superficially while the deeper parts underwent fatty degeneration resulting in a picture much like human atherosclerosis He noted that such plaques soon became pale as the haemoglobin was washed out of them, so confirming one of Duguid s earlier observations on human material

Harrison s experiments were repeated by *Thomas et al* (1956) in rabbits also fed on different types of fat In 50 per cent of animals the pulmonary arterial lesions contained fat droplets The purpose of the experiment was to demonstrate the theory of lipid infiltration of the intima but a totally unexpected finding was the presence of fat in the lesions of 50 per cent of the control animals on a fat-free diet a result more consistent with the thrombogenic theory of atherosclerosis since the lipid must have been endogenous in origin

XII

The Biochemical Approach

UNTIL recent years the application of chemical methods to the problem of atherosclerosis had yielded results that were conflicting and unpromising and mainly concerned with quantitative estimates of the cholesterol in the blood and the lipid and mineral content of the aorta

CHEMISTRY OF THE AORTA

Aschoff (1907) is often credited with the identification of cholesterol in atherosclerotic plaques but its presence in crystalline form was well known to Rokitansky and Virchow Employing whole aortas from atherosclerotic subjects *Baldauf* (1906) estimated the relative proportions of calcium neutral fat fatty acids and lecithin and *Windaus* (1910) showed that the cholesterol ester content was twenty times that of a healthy vessel *Schonheimer* (1926 1928) confirmed this observation using preparations of aortic intima and inner layer of media and maintained that his results favoured the theory of lipid infiltration since it was unlikely that such large amounts could be synthesized locally (It has been recently demonstrated by *Siperstein et al* (1951) in experimental animals that the aorta *is* capable of synthesizing cholesterol but only in small amounts)

Meeker and Jobling (1934) analysed 45 aortic plaques from different age groups and found that the total fat and total cholesterol increased with the severity of the atherosclerosis the most advanced lesions showed a rise in the proportion of free to esterified cholesterol The phospholipids remained constant throughout

Attempts have been made to establish the theory of lipid infiltration by comparing the cholesterol content of the plaques with the serum level In 147 aortas from previously healthy persons dying from trauma and other causes of sudden death *Lande and Sperry* (1936) were unable to show any correlation but *Weinhouse and Hirsch* (1940) found that the lipid proportions in the plaques themselves – as distinct from whole vessels – correspond closely to those of the serum This was also the experience of *McArthur* (1942)

Others have correlated changes in the chemistry of the *media* with advancing years Using micro-incineration methods *Ku* (1933) found a steady increase in calcium ash apparently derived from degenerate elastic fibres up to the end of the third decade after which the increase was irregular *Weinhouse and Hirsch* (1940) observed that the lipid content of the media also increased with age although neither the lipid nor the calcium in the media were proportional to the degree of sclerosis of the overlying intima They also made the observation that in the intima the cholesterol though enormously increased in fatty plaques is actually reduced in calcareous plaques (*Hirsch and Weinhouse* 1943)

Lansing et al (1948) applied the micro-incineration technique to the coronary arteries

and found that the increase in medial calcium started a decade earlier than in the aorta They believe that this process of elasto-calcinosis (not to be confused with Monckeberg s sclerosis) is the localizing factor in atherosclerosis a degenerative change due to age which not only precedes but is essential to the deposition of cholesterol in the overlying intima (*Lansing et al* 1950a and b) Their views are considered further under Arteriosclerosis and Atherosclerosis in Chapter XVII

Buck (1951) has shown that there is a logarithmic rate of increase in calcium magnesium and non-lipid phosphorus in the ageing aortic media The added mineral increase in atherosclerosis is relatively slight compared to the earlier age increase The degree of calcification may be missed in routine sections as calcium only stains with haemotoxylin in the presence of iron Thus micro-incineration is a more reliable guide *Buck and Rossiter* (1951) have observed that the total phospholipid content of the normal aorta rises with age largely due to an increase in sphingomyelin In atherosclerosis there is a further rise accompanied by an increase in lecithin Cephalin seems to play no part in lipid infiltration

THE SERUM CHOLESTEROL

Numerous assays of the serum cholesterol have been made with the aim of bringing human atherosclerosis into line with Anitschkow s experimental work but opinion differs sharply on the results According to *Mjassnikow* (1925) a pupil of Anitschkow hypercholesterolaemia is observed regularly in advanced atherosclerosis and in about half of the milder cases He therefore emphasized the importance of the cholesterol content of the diet in treatment *Rabinowitch* (1927 1929) also found a raised serum cholesterol in severe atherosclerosis but *Hunt* (1929) was unable to correlate the two

On the strength of the age factor in atherosclerosis (and disregarding the frequency of fatty streaking in young subjects) others have correlated serum cholesterol and age *Page et al* (1935) found no significant relationship but *Keys* and others of the Minnesota School (1949 1950a) found fault with their method of age grouping On the basis of 5000 measurements in both sexes of all ages Keys and his colleagues found a steady increase in serum cholesterol up to the age of 60 after which the curve tended to flatten and decline Exception might be taken to the selection of subjects for the 45-55 age group (who for reasons which are not made clear were chosen exclusively from local business and professional men in responsible positions) since others have suggested that there is an unduly high incidence of ischaemic heart disease in this social group at this age (*Ryle and Russell* 1949)

A more direct link between hypercholesterolaemia and coronary disease was revealed by *Davis et al* (1937) who found the average serum cholesterol in anginal cases higher than the control series in some cases far above the highest of the controls This was confirmed by *Morrison et al* (1948) who investigated 200 consecutive unselected cases of proved coronary occlusion (employing electrocardiography) Hypercholesterolaemia was present in 68 per cent of cases under 60 and 52 per cent of cases over 60 Essentially similar results were obtained by *Geier* (1949)

THE BIOCHEMICAL APPROACH

THE SERUM LIPIDS

However there is much to suggest – including experimental evidence to be quoted later – that while cholesterol infiltration of the intima may be a factor in atherosclerosis it is not achieved simply by overflow of excess lipids in the plasma and that there are other factors which may operate even in the absence of hypercholesterolaemia Among such factors those which have attracted most attention are (i) Chylomicrons (ii) Altered cholesterol/phospholipid ratio (iii) Altered lipoprotein ratio (iv) Giant molecules

(i) CHYLOMICROGRAPHY

Gage and Fish (19[illegible]4) described lipid particles which appear in normal plasma 1-[illegible] hours after the ingestion of food containing fat These are ½-1μ in diameter and are known as chylomicrons By giving a standard fatty meal and examining hourly samples of blood under dark ground illumination a curve can be plotted which indicates the frequency of these particles (*Frazer and Stewart* 1937)

Moreton (1947) showed that in conditions accompanied by hypercholesterolaemia – diabetes nephrosis myxoedema etc – the chylomicrons are unduly plentiful High speed centrifugation shows them to contain cholesterol triglycerides and fatty acids He therefore formulated a new theory of atherogenesis arguing that the accumulative effect of many fatty meals over a long period causes showers of lipid particles to appear in the plasma which are intermittently deposited in the tissue spaces of the intima The neutral fat and fatty acids are readily absorbed but the low solubility of the cholesterol causes it to remain even though the serum cholesterol has stayed within normal limits

Becker et al (1949) introduced the age factor noting that in the younger age groups the number of chylomicrons reaches its peak [illegible]½-3 hours after a fatty meal and returns to the fasting level in 5 hours in older subjects the peak which is much higher is reached in 8-12 hours and does not return to the fasting level for [illegible]4 hours

(ii) ALTERED CHOLESTEROL/PHOSPHOLIPID RATIO

It is a remarkable fact that the serum lipids do not form an emulsion and that the serum remains clear even in cases of hyperlipaemia *Ahrens and Kunkel* (1949) showed that this phenomenon was dependent on a corresponding rise in the serum phospholipid level and suggested that the phospholipids may help to stabilize the colloidal dispersion of plasma cholesterol They further noted a correlation between a raised cholesterol/phospholipid ratio and premature atherosclerosis These observations were confirmed by *Gertler et al* (1950a) and *Oliver and Boyd* (1953) in cases of myocardial infarction below the age of 40

(iii) ALTERED LIPOPROTEIN RATIO

The transparency of serum with a high lipid content had perplexed early observers and had led *Sørenson* (1931) to maintain that the phenomenon was explicable only by assuming linkage between lecithin and sterols on the one hand and the protein on the other These lipoproteins being water soluble may be concerned in the filtration and deposition of cholesterol in the intima

Two fractions have been identified in human serum by means of electrophoresis which causes them to migrate with the α- and β-globulins respectively (*Oncley et al* 1950) In healthy subjects the average ranges and ratios of the α- and β-lipoproteins as they have been styled have been determined (*Russ et al* 1951) Persons who have survived myocardial infarction or who have other definite evidence of atherosclerosis show a tendency to reduction of α-lipoprotein and an increase in β-lipoprotein (*Barr et al* 1951) These differences may be present even though there is no significant rise in the serum cholesterol and in patients with diabetes or nephrosis they are present before vascular complications are clinically recognizable

(iv) GIANT MOLECULES

Even more interest has been aroused by the work of *Gofman* and his colleagues in the University of California (*Gofman et al* 1950a and b) who in 1950 described cholesterol-bearing giant lipoprotein molecules in the serum of atherosclerotic patients with these characters

(1) They are not related to meals — i e they are not chylomicrons
(2) Their presence cannot be predicted from the serum-cholesterol level
(3) They are present with higher frequency in those who have survived myocardial infarcts also in sufferers from diabetes nephrosis hypothyroidism hypertension and cardiac ischaemia — i e all those conditions known to be associated with atherosclerosis

These molecules are not normally present in rabbit serum but they appear after cholesterol feeding A high concentration causes turbidity of the serum Their presence is revealed by ultracentrifugal flotation analysis and their rate of migration is expressed in Svedberg units which are determined by measurement of the refractive index gradient patterns Normal lipoprotein molecules are of the order of Sf 5-10 in atherosclerosis the larger Sf 10-20 class begin to appear

Gofman s view is that these giant molecules are responsible for the deposition of cholesterol in the intima and that atherosclerosis is associated with or caused by an error in the metabolism of fat and other lipids as distinct from hypercholesterolaemia alone It is too early to assess the value of these observations but already *Keys* (1951a and b) has objected that Gofman s normal ranges were from the 20-40 age group while the group with myocardial infarction ranged from 40-70 He therefore considers that the G substances (as he arbitrarily designates Gofman s giant molecules) are of no greater value than the serum cholesterol in the assessment of atherosclerosis since this too rises with age Indeed he denies that there is any evidence that the G substances indicate probability of present or impending coronary disease

Gofman et al (1952) and *Lyon et al* (1952) have replied citing abundant statistical evidence that the Sf 10-20 lipoprotein levels show at least a twofold and perhaps a tenfold higher relationship to atherosclerosis than the serum cholesterol does and that the slight relationship of the latter to atherosclerosis is by virtue of its partial correlation with the Sf 10-20

lipoproteins The using of coronary disease as their criterion of atherosclerosis may be of debatable validity

Further doubts have been thrown on Gofman's theories by *Paterson* (1954) who determined the serum cholesterol the cholesterol/phospholipid ratio and the Sf 10–20 lipoprotein molecules of patients before death and at subsequent autopsy found no obvious correlation between any of these and the degree of sclerosis or lipid content of their coronary arteries A similar discrepancy between lipoprotein molecular ranges and the degree of general atherosclerosis at autopsy was recorded by *Chapman et al* (1956)

This is the barest outline of these recent advances The whole subject of the relation of atherosclerosis to a disorder of lipid metabolism has been lucidly reviewed by *Gould* (1951) *Gutman* (1953) considers that the increase in Sf 10–20 lipoproteins β-lipoproteins and the cholesterol/phospholipid ratio are probably all facets of the same basic lipid disturbance

XIII

The Diet and Atherosclerosis

ALLIED to the biochemical approach is the dietetic one and animal feeding experiments have made it inevitable that human atherosclerosis should be attributed to the eating of foods rich in cholesterol (e g *Wacker and Hueck* 1913) These are chiefly eggs milk butter and other animal fats all cherished by civilizations with a high basic standard of living and reduced or absent in undernourished communities

Aschoff (1924) claimed that atherosclerosis decreased during the first World War when food rationing was universal in Germany However *Weiss and Minot* (1933) in a study of the racial incidence of atherosclerosis found no proof that overnutrition or malnutrition was a factor It was scarcely feasible to demonstrate experimentally induced atherosclerosis in human subjects but *Mjassnikow* (1925) and *Hunt* (1929) failed to raise the serum cholesterol by feeding cholesterol-rich foods to healthy individuals

The nearest approach to experimental atherosclerosis in man was cited by *Leary* (1936b) Reference has already been made to his theory that atherosclerosis is a disease of overcivilized communities where adults continue to eat in excess foodstuffs primarily intended for embryos and infants (i e milk and eggs) He claimed that from 1920 to 1930 when it was the practice to treat diabetics with a diet rich in cholesterol spectacular degrees of atherosclerosis became much commoner even in young subjects When this mode of treatment was abandoned the severity of the atherosclerosis became less

In a series of autopsies on Okinawans whose diet is largely vegetarian *Steiner* (1946) found that atherosclerosis develops late is of moderate degree and may be absent altogether Opinion varies on the relation of atherosclerosis to obesity which although not wholly a matter of dietetics may be briefly considered here *Dublin* (1930) quoted insurance company statistics to show that death from angina pectoris and other forms of arterial disease is two or three times as common in obese subjects as in those of normal or subnormal weight In 80 fatal cases of coronary disease in servicemen between 20 and 36 *French and Dock* (1944) found overweight the most striking single predisposing factor *Wilens* (1947a) found advanced atherosclerosis to be twice as common in obese subjects as in the poorly nourished groups His autopsy studies on the victims of wasting diseases suggested that loss of weight was accompanied by regression of atherosclerotic lesions (*Wilens* 1947b) However *Yater et al* (1948) found no correlation between obesity and coronary occlusion in the under-40 age group while *Faber and Lund* (1949) in a chemical assay of 400 aortas concluded that if hypertensive cases were excluded obesity bore no relation to the degree of atherosclerosis

Further statistical evidence was supplied by *Malmros* (1950) who found that during World War II the mortality from atherosclerosis and coronary disease decreased in Finland

Norway and Sweden where the consumption of eggs butter and other cholesterol-rich foods was reduced In Denmark where the total fat consumption declined but that of eggs and butter increased the death rate rose slightly In the United States where the consumption of eggs and milk increased (though butter was reduced) deaths from atherosclerosis steadily increased

But if dietary cholesterol is a factor in human atherosclerosis it is not just by causing hypercholesterolaemia *Keys et al* (1950b) and *Keys* (195-a) found that the consumption of a single large amount of cholesterol barely affects the serum level They also showed in a careful survey of 482 healthy adults over a period of 3 years that the serum cholesterol is not significantly related to the cholesterol intake in the diet *Gertler et al* (1950b) found this was also true of convalescent cases of myocardial infarction (presumably atherosclerotic subjects) *Wilkinson et al* (1950) similarly failed to find a clear relationship between the serum cholesterol and the total intake of carbohydrate fat protein or cholesterol in patients with familial hypercholesterolaemia

Theoretically of course there seems to be no reason to postulate a direct relationship between ingested cholesterol and the serum level since it has been shown experimentally that the mammalian liver readily synthesizes cholesterol from acetate (*Bloch and Rittenberg* 1942) It is also known that any mechanism which raises the blood fat (including ingestion of fat) will automatically elevate the serum cholesterol which functions as a vehicle for fatty acids (*Gubner and Ungerleider* 1949) The same lack of relationship between dietary intake serum cholesterol levels and the severity of atherosclerosis has been observed in cholesterol-fed rabbits (*Firstbrook* 1951)

Keys (195-b) dismissed Steiner s work on Okinawan autopsies as lacking in data on the diet and degree of atherosclerosis He harshly criticized Malmros s Scandinavian statistics as attempting to discover causation from a parallelism between crude estimates of national averages for two variables While agreeing that the serum cholesterol seems to be independent of the normal daily intake Keys showed in a series of human feeding experiments that a high fat diet raises the serum cholesterol and that on a fat-free diet the serum cholesterol is fairly rapidly reduced He therefore proposed that in the treatment of atherosclerosis the fats generally should be restricted and not cholesterol specifically

Controlled feeding experiments were carried out by *Morrison* (1952) on cases of ischaemic heart disease over a period of 3 years He found that in the group subsisting on a low-fat low-cholesterol diet the serum cholesterol was lowered by 30 per cent and that mortality was 14 per cent as compared with 30 per cent in the group on an unrestricted diet

In a recent speculative article *Sinclair* (1956) disputed Keys s view that the important factor in atherosclerosis is the total fat in the diet He claimed that what matters is the amount and structure of the dietary fatty acids which are altered by modern food-processing Oxidation of animal fats and hydrogenation of vegetable oils in the diet lead in the human consumer to the formation of abnormal cholesterol esters which are difficult to dispose of and so cause atheroma and abnormal phospholipids further contribute to coronary thrombosis by increasing the coagulability of the blood

Corroborative evidence has come from *Bronte-Stewart et al* (1956) who showed that animal fats and hydrogenated vegetable fat raise the serum-cholesterol whereas natural vegetable oils and the oil of marine animals do not

Fullerton et al (1953) prompted by Duguid s theory of atherogenesis studied the effect of fats on the coagulability of the blood It had long been known that the latter increases after meals (*Mills* 1923 *Mills and Necheles* 1928) and there was reason to believe that a lipid factor may be concerned in the process (*Macfarlane et al* 1941, *Waldron et al* 1951) Fullerton showed that post-prandial lipaemia is accompanied by an accelerated coagulation time and suggested that this was a factor in atherogenesis Discussing the apparent increase in coronary occlusions he adds It is important not to let this particular aspect overshadow the general problem the cause of its early and frequent localization in the coronary arteries may well be a problem separate from that of atherosclerosis in general

XIV

Inhibitory Factors

THE simple concept of atherosclerosis following hypercholesterolaemia due to an excess of cholesterol in the diet does not stand up to animal or human feeding experiments since it has been shown that there is no clear relation between dietary intake and serum levels nor according to some authorities (Keys is a conspicuous exception) between serum cholesterol levels and the degree of atherosclerosis. Experiments involving the use of various *inhibiting agents* indicate that hypercholesterolaemia may be a factor in cholesterol atherosclerosis but not necessarily the determining factor.

That experimental atherosclerosis can be inhibited in cholesterol-fed rabbits was first shown by *Murata* (1918) who succeeded in retarding or preventing the lesions by adding thyroid to the diet. *Liebig* (1929) produced a similar effect by the administration of iodine compounds. Both results were confirmed by *Turner* (1933) who also showed that the protective effect of potassium iodide is destroyed by thyroidectomy (*Turner and Khayat* 1933).

Since then a number of agents have been employed which are alleged to inhibit atherosclerosis (1) by preventing hypercholesterolaemia (2) by preventing deposition of cholesterol or (3) by lowering the frequency of the giant lipoprotein molecules.

(1) INHIBITION OF ATHEROSCLEROSIS BY PREVENTING HYPERCHOLESTEROLAEMIA

Kesten and Silbowitz (1942) found that soya lecithin fed along with cholesterol to rabbits prevents the usual hypercholesterolaemia and diminishes the incidence of atherosclerosis. *Adlersberg and Sobotka* (1943) added lecithin to the diet of human cases of hypercholesterolaemia over a period of several months and greatly reduced the serum level which rose again when the lecithin was withdrawn. A similar effect was noted in cases of coronary disease by *Steiner and Domanski* (1944). Experimental depression of the serum cholesterol in cholesterol-fed chicks has been recorded by *Peterson* (1951) using soya bean sterols.

Hermann (1946) claimed to have effected decholesterization of tissues (*a*) gradually by a low fat diet accompanied by thyroid extract and potassium iodide over a period of months or years (*b*) more rapidly by the administration of choline methionine inositol alcaucil or berenjena.

Bile is apparently necessary for the absorption of cholesterol from the bowel (*Siperstein et al* 1952) and as ferric chloride is known to precipitate bile salts *in vitro* this substance was fed along with cholesterol to birds resulting in a relative depression of the serum cholesterol and a reduced degree of atherosclerosis (*Siperstein et al* 1953).

Hopeful interest has been aroused by the discovery of *Pollak* (1953b and c) that sitosterol the stereo-isomer of cholesterol is not resorbed in the alimentary tract of rabbits or

Corroborative evidence has come from *Bronte-Stewart et al* (1956) who show animal fats and hydrogenated vegetable fat raise the serum-cholesterol wl vegetable oils and the oil of marine animals do not

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All those experiments in which the evidence for an inhibitory factor rests on a lesser degree of atherosclerosis in a treated group of rabbits as compared with a control series may have to be reassessed in the light of work by *Firstbrook* (1950) By feeding cholesterol to animals on graded diets he found a close relationship between the severity of the atherosclerosis and the relative gain in body weight He has objected therefore that the results of the alloxan-diabetes experiments of *McGill and Holman* and *Duff and McMillan* may be attributable not to an inhibitory effect but merely to loss of weight by the diabetic group of rabbits

XV

Contributory Factors

THESE are dealt with summarily because while interesting in themselves none of them has been seriously suggested as playing more than a secondary role in the genesis of atherosclerosis Age race physique and occupation being not so much single factors as a blending of multiple imponderable influences are not considered here and are best included with the statistical surveys

HYPERTENSION

In 500 consecutive cases of myocardial infarction *Master et al* (1939b) found this feature present in over 50 per cent of the male cases and 80 per cent of females The contributory influence of fluctuations in the blood-pressure in experimental atherosclerosis was noted by *Anitschkow* (1914) It is common experience that cases of prolonged hypertension rarely present in the autopsy room without severe atherosclerosis It is equally true however that both myocardial infarction and advanced atherosclerosis are very frequently encountered in subjects with a normal blood-pressure

DISORDERS OF METABOLISM

Conditions in which the plasma cholesterol is raised are usually characterized by severe atherosclerosis e g diabetes mellitus (*Rabinowitch* 1935) myxoedema (*Black and Campmeier* 1934) or familial xanthomatosis (*Muller* 1938) *Cook et al* (1947) recorded fatal coronary occlusion in a child of 13 suffering from xanthoma tuberosum

ENDOCRINE FACTORS

These are (*a*) thyroid (*b*) gonadal

(*a*) THYROID

The influence of the thyroid gland on experimental atherosclerosis has been mentioned (*Murata* 1918 *Turner and Khayat* 1933) and *Black and Campmeier* (1934) have reviewed the literature associating hypothyroidism with atherosclerosis and coronary occlusion *Lerman and White* (1946) observed a low basal metabolic rate and a raised serum cholesterol in persons under the age of 40 suffering from cardiac ischaemia

In the experimental field *Shapiro* (19-7) found that thyroidectomy accelerated cholesterol atherosclerosis in rabbits *Steiner and Kendall* (1946 1949) were able to induce

cholesterol atherosclerosis (and coronary occlusion) in dogs – normally resistant to feeding experiments – by administering thiouracil *Friedman et al* (1952) found that in rats this drug reduced the rate of cholesterol excretion thus allowing more to be resorbed in the blood-stream while the giving of thyroid extract had the reverse effect The possible relation of diminished thyroid activity to hypercholesterolaemia in the older age groups has not escaped notice

(*b*) GONADAL

The influence of gonadal disturbances as a contributory factor in atherosclerosis has aroused further speculation The inchoate evidence derived from experimental and human material may be summarized under the effects of (i) Castration (ii) Oestrogen administration (iii) Androgen administration

(i) *Castration*

Murata and Kataoka (1918) found that castration accelerates the development of atherosclerosis in cholesterol-fed rabbits an observation confirmed by *Chuma* (1923) and *Shapiro* (1927) *Rivin and Dimitroff* (1954) observed a raised incidence of atherosclerosis in autopsies of females who had undergone bilateral oophorectomy

(ii) *Oestrogen administration*

The last-mentioned authors also noted a diminution in atherosclerosis in autopsies on males treated with oestrogens for prostatic cancer *Barr et al* (1952) noting that women of the child-bearing age are relatively immune to cardiac infarction treated a series of patients convalescing from this condition with oestrogens and observed a reduction in the serum cholesterol and in the β-lipoproteins *Furman et al* (1954) noted a corresponding rise in the α-lipoproteins in post-menopausal females treated by oestrogens the β-lipoproteins were barely altered

Curious but interesting results have been obtained experimentally with cockerel chicks *Katz* (195[illegible]) found that implanted oestrogens cause hyperlipaemia and *increased* atherosclerosis In cholesterol-fed cockerels however while failing to check *aortic* atherosclerosis oestrogens apparently inhibit *coronary* atherosclerosis or cause regression of this condition if already established even in the presence of hyperlipaemia (*Pick et al* 195[illegible]a and b) These authors draw the significant conclusion that atherogenesis does not proceed according to the same biological laws in different vascular beds

(iii) *Androgen administration*

Furman et al (1954) have observed that the serum of eunuchoid males treated by androgens shows a lowering of the α-lipoproteins

From the foregoing there seems to be some justification for adding oestrogens to the list of Inhibitory Factors in human atherosclerosis

XVI

The Statistical Approach

DISEASES of high frequency but obscure pathogenesis (e g cancer peptic ulcer etc) are *inevitably subjected sooner or later to statistical surveys* and in recent years coronary disease has also been attacked on this front The investigations have been chiefly concerned with (*a*) the increased frequency of coronary disease and (*b*) the type of individual who suffers from it

(*a*) INCREASED FREQUENCY OF CORONARY DISEASE

Whatever may be the truth about coronary sclerosis there seems to be little doubt that atherosclerosis is as old as human history as was shown by the work of *Shattock* (1908) and *Ruffer* (1911) on Egyptian mummies Ruffer examined a sufficient number to enable him to conclude that atherosclerosis in the aorta and limbs (the coronary arteries unfortunately had been removed with the rest of the viscera) had the same distribution gross characters and microscopic appearance in 1500 B C as it has today and that the disease was probably as common in ancient Egypt as it is in modern Western civilization Most of the mummies were members of the priesthood who according to Ruffer probably ate richly and shunned heavy manual work

Anatomists have been familiar with atherosclerosis since the seventeenth century and probably earlier but as we have seen they were slow to recognize coronary occlusion For this reason *Osler s* concern over the increased incidence of angina pectoris may have been no more than increased awareness of a common but undiagnosed condition and it can be fairly presumed that a great many deaths certified in his day as myocardial degeneration chronic myocarditis and old age were in fact directly attributable to coronary occlusion

More recently however it has been felt that even allowing for improved diagnosis and increased expectation of life mortality from coronary disease is definitely increasing *Ryle and Russell* (1949) in a full statistical review showed that the mortality in people over the age of 35 was *15 times* greater in 1945 than in 1921 especially in the 40-55 male age group and particularly among the higher income groups

Between 1938 and 1948 the mortality doubled (*Morris* 1951) Now while it might be argued that in 1921 the disease was not sufficiently widely recognized it is difficult to believe that this was so in 1938 Morris found that autopsy records at the London Hospital revealed no increase in *atherosclerosis* of the coronary arteries since 1908 although clinical coronary thrombosis had greatly increased a paradox which suggested that more attention should be given to the occurrence of thrombosis than to atherosclerosis alone

(*b*) THE TYPE OF INDIVIDUAL AFFECTED

A very early reference to the predilection of coronary disease for a social group is contained in an article by *Curtin* (1897) who noted the frequency of angina pectoris in doctors *Osler* (1910) thought it affected the better classes generally and recalling that it had claimed such distinguished leeches as Hunter Charcot and Pepper said that angina pectoris might be called the *morbus medicorum* Though this was subsequently dismissed as the illusion of a successful physician with a clientele preponderantly affluent confirmation has since come from the Registrar General s Reports which show that medical men have an incidence far higher than any other profession and immeasurably higher than that of heavy manual workers (*Conybeare* 195-)

It is a commonplace to associate coronary disease with what is vaguely described as stress or (as if it were more precise) stresses and strains without further definition of these terms Certainly violent physical effort has been known to precipitate sudden death in individuals with coronary occlusion but statistically manual workers who for economic reasons must go on working after an attack of coronary thrombosis have a better expectation of survival than white-collar workers (*Phipps* 1936)

Master et al (1937b 1939a and b) found that coronary thrombosis occurs in all walks of life and all types of occupation They failed to find a significant correlation between coronary disease and physical exertion excitement infection tobacco meals the time of day or the season of year In fact the only significant aetiological factor was the sex of the individual since the incidence in males compared with females was 3 4 1 The difference in the incidence of coronary disease between men and women of the sixth decade is particularly striking (*Ackerman et al* 1950 *White et al* 1950 *Firstbrook* 1951) The possibility that oestrogens exercise an inhibitory influence in women has already been commented on

Ryle and Russell (1949) found that the increase in middle-aged men is significantly greater than in women of like age and suggested an occupational or sociological influence In the social class which incorporates professional workers and business men with administrative responsibilities the mortality of the 40-55 age group is ten times that of their wives *Stocks* (1951) confirmed Phipps s views by showing that only 14 8 per cent of cardiac deaths among heavy manual workers are due to coronary occlusion as compared with 38 6 per cent in the white-collar class

Recently *Morris et al* (1953) have produced evidence suggesting that individuals in sedentary occupations are more prone to coronary disease than their more active fellows *Arnott* (1954) thinks that stress is a fallacy the fact being that patients prefer to be told that they are the victims of strain rather than of gluttony or physical indolence

The statistical approach has revealed significant data relating to males who develop coronary disease at a relatively early age *Yater et al* (1948) analysed a large series (866) of American service men below the age of 40 suffering from coronary disease The incidence in negroes was only two-thirds of that in Caucasians Obesity was not a significant factor Yater and his colleagues were impressed with the hereditary factor which emerged from a study of the family histories *Adlersberg et al* (1949) also found a familial

relationship in coronary disease suggesting a hereditary hypercholesterolaemia especially in patients under 50 A genetic analysis of 35 families suffering from xanthomatosis indicated that the disturbance of cholesterol metabolism is inherited as an incomplete dominant trait *Duff and McMillan* (1951) are inclined to regard hypercholesterolaemic patients with premature coronary disease as a distinct group not representative of the generality of atherosclerotic subjects

An even more elaborate statistical survey of coronary disease in young adults has recently been compiled by *Gertler and White* (1954) who introduce biometric methods in their calculations Young coronary disease patients are usually endomorphic mesomorphs and the physically oestrogenic type of male is less prone to cardiac infarction than his more robust brother Reviewing recent researches on serum lipid chemistry these authors conclude that it should now be possible to pre-select coronary-prone individuals from the population Pending fuller clarification of these matters however the thoughtful physician might well question the advisability of acting on this suggestion

The subject of racial incidence involving as it does questions of heredity diet economic and social habits is debatable Since *Osler's* day Jews have been said to be singularly prone to coronary disease Asiatic peoples to be the reverse Recently *Bronte-Stewart et al* (1955) observed that the Europeans of Cape Peninsula had a higher incidence of coronary disease than the native Bantus while the Cape Coloured occupied an intermediate position The incidence ran parallel to the serum cholesterol and β-lipoprotein levels in the three groups and the team (of which *Keys* was a member) detected a similar relationship to the fat intake of their respective *diets* thereby suggesting that the differentiating factors *are not so much racial as social and economic* However until the problem has been tackled on a world-wide scale it would be wiser to reserve judgment

XVII

Local Predisposing Factors

THE biochemists and statisticians have carried their investigations sufficiently far from the atherosclerotic plaque for a morbid anatomist to appreciate the sardonic comment of *Duff and McMillan* (1951) that the casual reader of recent literature might wonder whether some authors conceive of an atherosclerosis so independent of the vessel wall that it may occur in the absence of the blood-vessels themselves

It is true that while more is being learned yearly about the type of individual who dies prematurely of coronary occlusion, and the alterations in the blood-chemistry that predispose to this event little progress is being made in finding an answer to two crucial questions What determines the localization of atherosclerotic plaques generally And why in particular are the coronary arteries so frequently involved

Arguments on these subjects have been and still are largely theoretical or based on flimsy evidence Reference has been made to the hypotheses of *Rindfleisch* (haemic currents) *Thoma* (medial bulging) *Aschoff* (overstretching) *Duguid* (shearing stress) *Ssolowjew* (local trauma) and *Harrison* (abnormal movement of the underlying media) None of these affords a comprehensive explanation of all the established data

ATHEROSCLEROSIS AND ARTERIOSCLEROSIS

The fact that atherosclerosis can be readily produced experimentally in previously healthy arteries by feeding cholesterol to animals has tended to obscure the question of underlying pre-existing arterial changes in the human subject The added fact that fibro-elastic proliferation rarely occurs in the human intima in the absence of atheromatous plaques has led to its being neglected in the consideration of atherogenesis

In recent years however interest has been revived in the existence of arteriosclerosis as a separate if not independent entity from atherosclerosis It will be recalled that both *Jores* and *Aschoff* had emphasized the changes in the elastic layer and intimal ground substance which in their view preceded the deposition of lipids the former regarding the process as pathological (*Jores* 1924) the latter as the physiological process of ageing (*Aschoff* 1924)

Thoma's theory that the plaques were secondary to a loss of medial elasticity has lately been reinstated *Blumenthal et al* (1944) using the micro-incineration technique found that medial calcification preceded the formation of intimal plaques and observed a relationship between calcification loss of elasticity and increasing age They believe that elastic fragmentation and medial calcification are age changes which result in dilatation of the vessel and that the intimal plaques are secondary (*Blumenthal et al* 1950) A somewhat similar view is shared by *Crawford and Levene* (1953)

Lansing and his associates followed up this work by showing that while the calcium content of the media increases with age the elastin content is barely altered—i e the loss of *elasticity* in an ageing vessel is not accompanied by loss of elastic tissue (*Lansing et al* 1950a) But age alone is not the cause of atherosclerosis since medial calcinosis and atherosclerosis are not found in the pulmonary arteries of elderly subjects unless there is some unnatural stress such as pulmonary hypertension (*Lansing et al* 1950c)

This school defines atherosclerosis as a process involving fatty and fibrotic degeneration of the intima of vessels arteriosclerosis as an age-dependent process of fatty and fibrotic degeneration of the intima accompanied by and generally preceded by calcification of the medial elastic tissue (*Lansing et al* 1950a) They insist however that these views in no way involve a rejection of the theory of disordered lipid metabolism as a factor in atherosclerosis

Lansing (1952) deliberately uses the term ageing to cover not only the passage of time but exogenous insults to the vessels *Moschcowitz* (1950) wisely believes that in this respect it is impossible to say where normal ageing ends and disease begins He regards the hyperplastic changes as an adaptation to rising intra-arterial pressure from birth to old age and concludes that atherosclerosis cannot be considered as synonymous with arteriosclerosis since it is not primary and lacks the consistent morphologic and/or pathogenetic background of hyperplastic arteriosclerosis At best it is only a part or a facultative lesion of arteriosclerosis

MUCINOUS DEGENERATION AS A LOCALIZING FACTOR

Virchow (1856) observed a gelatinous swelling of the intima preceding atherosclerosis and *Saltykow* (1908) found mucoid degeneration of the collagen in relation to the lipid deposits of cholesterol atherosclerosis *Bjorling* (1911) described a metachromatic mucinous material in the ground substance of the intima and media of normal arteries which was greatly increased in arteriosclerosis It bore a special relation to the elastic fibres *Schultz* (1922) made similar observations on this substance and noted its affinity for lipids and calcium

These discoveries received little attention until 1949 when *Faber* traced a connection between cholesterol deposits and ageing or diseased tissues containing a substance that stains metachromatically with methylene blue and which he believed to be a sulphate-containing polyuronide In the human aorta he was able to trace a progressive increase in this material with the age of the subject and he advanced a theory that it acted as a localizing factor in the subsequent deposition of cholesterol In hypertensive or luetic aortas this material is present in even greater amounts corresponding to the increased cholesterol

Rinehart and Greenberg (1949) observed an increase in a basophilic mucoid material with the staining reactions of a mucopolysaccharide in the intimal ground substance of monkeys suffering from experimentally induced pyridoxine deficiency In prolonged experiments (which incidentally do not involve the feeding of cholesterol) lipids accumulate in these mucoid areas resulting in typical atherosclerotic plaques (*Rinehart and Greenberg* 1951) While these authors do not claim that pyridoxine deficiency is the cause of human athero-

sclerosis they consider that the morphology and distribution of the monkey lesions bear a much closer resemblance to their human counterparts than does cholesterol atherosclerosis (*Rinehart* 1954)

Moon and Rinehart (1952) observed an increase in mucoid ground substance in the intima and media of early lesions in human coronary arteries accompanied by a fragmentation and degeneration of elastic tissue This is followed by proliferation of collagen and elastic fibres and the deposition of cholesterol in the deeper layers presumably carried there by the vasa vasorum and not through the intima Calcification intramural haemorrhage and thrombosis are all late complications

Small amounts of the mucoid substance are present in the normal aorta both in the *intima and surrounding the elastic fibres of the media acting both as a cement and as a* matrix in which these fibres glide (*Rinehart and Abul-Haj* 1951) It is suggested that it may be a mother-substance from which collagen and elastin are derived At all events it appears to have an affinity for the serum lipids

OTHER LOCALIZING FACTORS

Most of the evidence from the isolated observations quoted below is derived from experiments which involve only one type of animal or from the use of traumata with no parallel in human atherosclerosis For example *Paterson et al* (1948) have shown that spontaneous hydropic degeneration of the *media* occurs in the coronary arteries of certain breeds of chicken accompanied by secondary atherosclerosis Feeding of cholesterol causes more lipid to be deposited at the site of these spontaneous lesions Again *Taylor et al* (1950) and *Kelly et al* (1951) have confirmed Ssolowjew s experiments by first freezing segments of the rabbit s aorta with a cold needle and then feeding cholesterol The lipid is deposited over the traumatized segments

However medial disease as a precursor of human atherosclerosis (e g in syphilitic aortitis) has long been recognized The objection to the experiments quoted is that (*assuming fatty streaking is an early form of atherosclerosis) they fail to explain the early* intimal lesion occurring in the absence of demonstrable medial disease In short they do little more than establish the fact that the deposition of cholesterol may be determined by local factors without revealing what those factors are

As regards *coronary* atherosclerosis *at least one localizing factor may have been explained* by *Geiringer* (1951b) who showed that one in five coronary arteries runs for all or part of its course within the substance of the myocardium Such vessels have a thinner intima than their epicardial counterparts and atherosclerosis is much less common in them This lends support to *Leary s* view (1936a) that contraction o*f the ventricles compresses the* distal (or intramural) portions of the coronary vessels so imposing an unnatural strain on the proximal epicardial segments during systole

Mention has been made of the theory of *Dock* (1946) who considers that the unusual thickness of the coronary intima even at birth predisposes to atherosclerosis in later life *Wilens* (1951) has observed diffuse intimal thickening in other arteries prone to athero-

sclerosis which he thinks is not a natural development but is related to the same mechanism that causes the plaques

His earlier work also deserves comment He found that loss of elasticity in the human aorta is directly related to the age of the subject and that the earliest and largest lipid deposits occur in areas most subject to loss of recoil He therefore suggested that lipid infiltration of the intima is related to immobility of the vessel wall (*Wilens* 1937) In Chapter IV I referred to the work of *Harrison* (1939) who induced arterial dilatation (and presumably diminished movement) by lumbar sympathectomy and found more severe atherosclerosis in the leg arteries on the affected side *Wilens* (1942) fitted silver cuffs round the carotid and femoral arteries of rabbits to render the enclosed segments less mobile and observed that cholesterol feeding causes more extensive lipid deposits in the immobilized vessel than elsewhere in the arterial tree

Enough has been written of the historical background the scientific literature and the conflicting theories concerning the pathogenesis of coronary sclerosis enough at any rate to indicate the importance of the thrombogenic hypothesis with which Part Two of this work is largely concerned

PART TWO

A STUDY OF THE MORPHOLOGY OF CORONARY OCCLUSION

XVIII

Methods and Materials

THE next eight chapters are devoted to a histopathological study of coronary occlusion The work was originally undertaken in an attempt to assess the role of capillary haemorrhages in atherosclerotic plaques as a factor in coronary occlusion (*Paterson* 1936) and to examine the thrombogenic hypothesis of *Duguid* (1946) – a viewpoint it must be admitted which at the outset the present author was reluctant to accept

It was felt that a three-dimensional picture of the more seriously diseased segments of occluded coronary arteries might best be obtained by serial sections and differential staining Similar methods had been employed by previous investigators but on a smaller scale and with limited objectives It was also considered advantageous to try to assess the extent and degree of atherosclerosis *in the whole coronary tree and to compare these* with the condition of the rest of the cardiovascular system Thus Chapters XXV-XXIX contain a rough attempt at correlation between coronary atherosclerosis and the state of other visceral and skeletal arteries the condition of the kidneys cardiac weight and myocardial infarction

For the purpose material was collected from 40 consecutive cases of advanced coronary disease Thirty-eight died of coronary insufficiency 2 of unrelated causes (No 3 spontaneous rupture of the aorta No 18 carcinomatosis and bronchopneumonia – see Table B) Twenty-six of the 38 were cases of sudden death 22 being ambulant individuals who died at home at work in the street in the ambulance or within an hour of admission to hospital these were examined on instructions from the Coroner The other 4 sudden deaths were in hospital during convalescence from other illnesses (No 9 chronic nephritis No 11 gastrectomy for peptic ulcer No 14 pneumonectomy for carcinoma No 25 diabetes myxoedema and hypertension) The remaining 12 were examples of gradual death from coronary disease – i e dying in hospital some days or weeks after a heart attack

At first it was felt that the cardiovascular system of those dying suddenly would yield more accurate information on the pathology of acute coronary insufficiency than those dying with myocardial infarcts some days or weeks later where extensive thrombosis is the rule but the advantages of examining and comparing both types were rapidly appreciated In all 116 blocks of coronary artery were sectioned serially and some 5700 sections examined Their distribution as to the branch affected and the type of death is shown in Table C

It is important to remember that although the whole coronary tree was examined macroscopically the microscopic study was confined to segments wholly occluded or severely narrowed and did not cover early lesions It is therefore concerned with the

serious late effects of coronary atherosclerosis and only indirectly with the much wider problem of atherosclerosis

TABLE B

Case No	Sex	Age	Type of Death	Block Sectioned Serially: L. Cor Trunk	L A D B	L Circumflex	R Cor	Other Autopsy Findings
1	M	50	Gradual	—	1	—	—	Cerebral embolism Bronchopneumonia
2	M	51	Sudden	—	1	—	—	—
3	M	67	Other causes	—	3	—	1	Spontaneous rupture of Aorta
4	M	66	Sudden	—	3	—	1	—
5	M	54	Gradual	—	1	—	1	Malignant hypertension and uraemia
6	M	55	Sudden	—	1	—	1	Chronic pulmonary tuberculosis
7	M	74	Sudden	—	—	—	4	—
8	M	4[illegible]	Gradual	—	—	—	—	Hypertension and pulmonary oedema
9	M	48	Sudden	—	1	—	—	Ellis type II nephritis hypertension syphilitic aortitis
10	M	68	Sudden	—	—	—	2	—
11	F	68	Sudden	—	1	—	—	Post gastrectomy
12	M	75	Sudden	—	—	3	—	Myomalacia cordis and haemopericardium
13	M	59	Gradual	—	—	2		Multiple infarcts
14	M	55	Sudden	—	—	—	1	Post pneumonectomy
15	M	78	Sudden	—	—	1	1	—
16	F	6[illegible]	Gradual	—	2	—	3	Multiple infarcts
17	M	54	Sudden	—		—	—	—
18	F	70	Other cause	—	2	—	2	Melanoma of eye with multiple metastases Pneumonia
19	M	70	Sudden	—	—	—	—	—
20	M	37	Gradual	—	4	—	3	Multiple infarcts
21	M	64	Sudden	—	1	2	—	Diabetes mellitus
22	M	58	Sudden	—	—	1	1	—
23	F	74	Gradual	—	—	—	—	Diabetes Infarct of brain
24	M	75	Sudden	—	2	—	—	—
25	F	5[illegible]	Sudden	—	—	2	5	Diabetes myxoedema hypertension
26	M	67	Sudden		—	—	—	—
27	M	59	Sudden	—	—	—	1	—
28	M	66	Gradual	—	6	—	2	Post prostatectomy Hypertension
29	M	6[illegible]	Sudden	—	—	—		—
30	M	71	Sudden	—	4	—	—	—
31	M	51	Sudden	—	6	—		—
32	M	47	Sudden	—	3	2	—	—
33	M	59	Gradual	—	1	1	3	Acute gastric ulcer
34	M	53	Sudden	—	2	—	5	—
35	M	80	Gradual	—	—	—	4	Myomalacia cordis
36	M	48	Gradual	—	—	—	1	Hypertension
37	F	64	Sudden	—	1	—	—	—
38	M	63	Sudden	—	—	1	—	—
39	M	67	Gradual	—	—	—	1	Hypertension
40	M		Sudden	—	1	—	—	
				2	50	15	49	

TABLE C

	Sudden Death	Grad al De th	Death from Other Causes	Tot ls
No of Cases	26	12	2	40
No of Blocks	70	38	8	116
L Co (Trunk)	2	—	—	2
L A D B	30	15	5	50
L Circumflex	12	3	—	15
R Cor	26	20	3	49

PROCEDURE

During the autopsy the coronary arteries were subjected to as few cuts as possible in establishing the cause of death These were made at right angles to the long axis of the vessel and opening the artery by slitting along its lumen with fine-pointed scissors was expressly avoided since this method as *Marie* observed as long ago as 1896 is liable to dislodge an unsuspected thrombus not to mention the further disadvantages of damaging the vessel lining and destroying the continuity of the vascular coats in the subsequent microscopic examination

The heart was then weighed packed with cotton wool soaked in 5 per cent formol-saline and fixed along with the whole aorta and segments of visceral and peripheral arteries The choice of brachial popliteal and renal arteries for comparison was to some extent arbitrary but to give some sort of uniformity the limb arteries were always removed at the same level – i e that of the adjacent joints – and the renal artery sampled in its middle third

When completely fixed the coronary arteries were examined throughout their epicardial course by making a series of slices at right angles to the long axis of the vessel at intervals of approximately 5 mm Diseased segments were listed under one of the following headings

1 Left Coronary Artery (main trunk)
2 Left Anterior Descending Branch
3 Left Circumflex Branch
4 Right Coronary Artery and its Main Branches

Those slices showing gross narrowing or occlusion by atherosclerosis intimal haemorrhage or thrombosis were then transferred to Perenyi s Fluid* (to facilitate decalcification) a note being kept of their sequence and the distal aspect of each block of tissue being identified by a short loop of horsehair threaded through the fat or muscle surrounding the artery This ensured that all segments were blocked with the proximal surface towards the cutting end of the block

After decalcification the vessels were processed in the usual way and blocked in paraffin.

* See Append x

In this manner it was possible to cut serially through several blocks comprising a diseased stretch of artery perhaps several centimetres in length, and with a minimum of tissue loss Most of the occluded segments could be included in the course of two or three blocks less commonly six to eight were necessary

Serial sections were then cut at 5μ and every sixth section mounted the remainder being preserved between sheets of paper for future use if required Each slide could conveniently accommodate three sections and as six different stains were employed the sections were mounted in batches of eighteen in the following manner

(1)	(2)	(3)	(4)	(5)	(6)
1	7	13	19	25	31
37	43	49	55	61	67
73	79	85	91	97	103

It was appreciated from the outset that haematoxylin-eosin is an inadequate stain for vessels generally and for atherosclerotic arteries in particular Muscle elastic fibres collagen reticulin fibrin conglutinated red cells – all stain an almost uniform red colour and the varied nature of an intimal deposit may be overlooked as shown in Figs 5-6

As there is no one stain which reveals all the elements involved normal and abnormal the following were employed in regularly recurring series

Haematoxylin-eosin
Sheridan s elastic stain*
Periodic Acid-Schiff
Heidenhain s Azan
Foot s Silver Impregnation
Phosphotungstic Acid-Haematoxylin

In the first few blocks examined the Benzidine and Prussian Blue reactions were employed routinely but the practice was discontinued in view of the limited or redundant information they yielded

It will be seen that the mounting of every sixth section cut at 5μ means that it is possible to compare differently stained sections at intervals of 30μ throughout the block proceeding along the vessel in a distal direction The average block yielded about 100 sections by this reckoning

The comparison was effected by means of a comparator eyepiece mounted on two microscopes (Fig 4) the two images occupying their respective halves of the visual field (see Frontispiece) Equivalent areas of consecutive sections differentially stained could then be studied at varying magnifications without the observer having to depend on the memory of a visual image and without undue ocular strain

This method enables one to construct a three-dimensional image of the elements involved in repair recanalization anomalous vascularization intimal haemorrhages lipid accumulations calcified plaques fibrinous encrustations mural thrombosis etc The

* See Appendix

absence of fat staining is an undoubted flaw in the method but for the present purpose it would have been impossible to maintain and follow the continuity of the finer structures by any other method than that employed

In each case the thoracic and abdominal aorta were sectioned and in the great majority the brachial popliteal and renal arteries Where necessary a similar technique of serial section was employed but in the aorta and other arteries where serious narrowing is not a feature *the various accidents and adaptations in the diseased intima are less complex* and can be conveniently studied by a single set of six serial sections stained differentially

The appearances in the coronary arteries are described first To facilitate descriptions which are apt to be tedious numerous photomicrographs are appended and these form an integral part of the argument The wide variety of the microscopic lesions makes it impossible to assess the frequency of each in terms of percentages and it is hoped that the volume of material examined will be considered a mitigating feature for the use of such vague terms as frequently sometimes rarely etc

In this manner it was possible to cut serially through several blocks comprising a diseased stretch of artery perhaps several centimetres in length and with a minimum of tissue loss Most of the occluded segments could be included in the course of two or three blocks less commonly six to eight were necessary

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* See Appendix



Fig 5
Anterior descending branch L coronary artery Gro s gn t ring deformity Case 31 H E × 25



Fig 6
Same essel, showing h matom m the plaqu Az n × 25



Fig 7
Ad ent tial congestion n s ere coronar occlu on. L A D B Case 11 PTAH × 18



Fig 8
Perivascula lymphocytosis of ad entitia R. Cor Case 4 H E × 70



Fig 9

Atheromatous abscess in dventit a surrou ded by foam cells and altered blood pig nent R Co Case 18 H E × 65

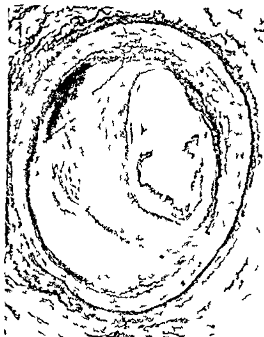


Fig 10

Atrophy of media at b se of plaq e R Cor Case 34 Sheridan × 30

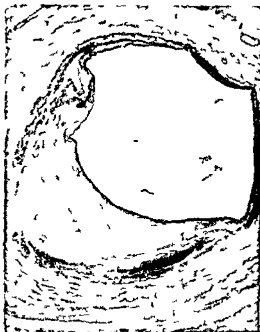


Fig 11

Gap in media at base of plaque L Circumflex Case 25 PAS × 30



Fig 12

F ee va cular co munication through gap in med L. Circumflex Case 25 A an × 30

similarly affected The significance of this is difficult to assess particularly in relation to syphilis The lesions were scanty compared to the extent and distribution of atherosclerosis and were not related to the main coronary orifices in the aorta

In many cases there was no other evidence of syphilis clinically serologically or in the aorta or other arteries and such a diagnosis would have to rest on the appearances in the coronary vessels alone With such a chronic and pervasive infection as syphilis rigid exclusion of the diagnosis is hardly possible but in the total absence of lesions elsewhere it seems more likely that the infiltration is a low-grade reaction to the atherosclerotic process possibly concerned in the scavenging of degenerate material

Horn and Finkelstein (1940) observed similar lymphocytic accumulations and unless these were accompanied by endarteritis of the vasa they were regarded as non-syphilitic These authors pointed out that in four of their cases of syphilitic aortitis the coronary vessels showed simple atherosclerosis only It has also been my experience that adventitial lymphocytosis can occur in definitely non-syphilitic conditions notably the arteriosclerotic aneurysms of larger arteries where it appears to be an inflammatory reaction to the subjacent thrombosis

RARER LESIONS

Hæmorrhage into the adventitia was observed only once in a hypertensive female aged 61 with a dissecting aneurysm of the media of the left coronary artery A somewhat similar case was recorded by *Uehlinger* (1947) On another occasion a form of atheromatous softening in all respects resembling an atheromatous abscess was found in the adventitia (Fig 9) apparently right outside the vessel but this was shown a few sections later to communicate with a similar lake of altered blood and lipid in a large intimal plaque from which it had been extruded through a small gap in the degenerated media The only reference encountered in the literature relating to lesions of this type was a paper by *Levy* (1936a) who recorded an atheromatous abscess of the *aorta* which ruptured through the adventitia and caused death

CHANGES IN THE MEDIA

These are (*a*) Atrophy (*b*) Penetration by hypertrophic vasa vasorum

(*a*) ATROPHY

The late results and complications of atherosclerosis are to a great extent determined by the width of the vessel involved In the aorta atheroma is largely confined to the intima and does not encroach seriously on the lumen Some degree of fibrous replacement of the musculo-elastic tissue is sometimes noted in the superficial (i e innermost) media just below the plaque but only in very advanced cases is this sufficient to cause serious weakening and it is generally agreed that neither dissecting aneurysms nor arteriosclerotic aneurysms are due to atheroma *per se* but to degenerative changes in the medial muscle or elastic

In coronary atherosclerosis however the base of an intimal plaque is much larger in relation to the circumference of the vessel at once causing narrowing of the lumen and

disuse atrophy of a large part of the media The degree of medial atrophy is considerably less conspicuous in haematoxylin-eosin preparations than in sections selectively stained to show up muscle or elastic fibres

These reveal that the atrophy is usually co-extensive with the intimal plaque (Fig 10) or diffuse if the intima is thickened uniformly Over the thickest part of the plaque the media may be absent altogether (Fig 11) or represented by the approximated layers of the internal and external laminae only When this occurs there may be a very free communication between the adventitial vasa and the vessels in the plaque (Fig 12)

It is inconceivable that the atrophied media splinted by a rigid plaque of intimal fibrosis perhaps six or eight times as thick as the media itself should be capable of contraction and it is thus probable that *disuse* is a major factor in causing the atrophy In some instances however degenerative swelling of the plaque especially if deeply placed and calcareous appears to be capable of exerting direct pressure on the adjacent media resulting in focal atrophy An extreme example of pressure atrophy due to focal calcification is shown in Fig 13

Crawford and Levene (1953) have argued that if the atrophy is due to disuse the media should be thinned without being bulged outward by the plaque and that as the only pressure to which the media is subjected comes from the lumen the interposition of an atherosclerotic plaque cannot increase the pressure to which the media is exposed These arguments do not take sufficient account of the fact that any muscle will atrophy if it is denied the power to contract and that once weakened in this way it is liable to stretch

(*b*) PENETRATION BY HYPERTROPHIC VASA VASORUM

Though seldom encountered in single routine sections a very constant feature of diseased coronary arteries is the periodic interruption of the media by abnormally large vasa vasorum The prominence of the adventitial vasa has already received comment and their penetration of the media is merely a stage in their passage to or from the thickened intima Their significance will be more fully discussed in a later section

In the healthy media the vasa are quite inconspicuous and require special injection techniques for their demonstration *Woodruff* (19-6) and *Robertson* (1929) although differing slightly on the depth of penetration were agreed that the vasa normally stop short of the internal elastic lamina and that the intima is nourished directly by the blood in the lumen The extensive literature on this aspect of the subject has been ably condensed by *Ramsey (1936)*

In atherosclerosis however the penetrating vasa may be wider than the media itself (Fig 14) a phenomenon frequently exaggerated by the corresponding atrophy of the latter In fact *Geiringer* (1951a) holds that the gaps so created are capable of weakening the media and in the example illustrated in Fig 12 this may be true But a hiatus of such magnitude is rare and even with the smaller ones a false impression may be gained from a two-dimensional cross-section The media immediately proximal and distal to the average gap *is intact and these infrequent breaches represent* no more than a few minute and widely separated perforations in a substantial layer of muscle and elastic



FIG 13

Fo l calcif cat on u ing p e u atrophy of med a R Cor Case 35 PTAH × 30



FIG 14

Hype t ph d v b hing t oph d ı d a t jo n a crescent of e sel t b se of pl que L A D B C se 16 PAS × 45



FIG 15

Normal o ona y tery f om a femal aged 31 who d ed of m lt pl inju es H E × 135



FIG 16

S gn e-n g d fo m ty showing l yering R Co Case 5 Sheridan × o

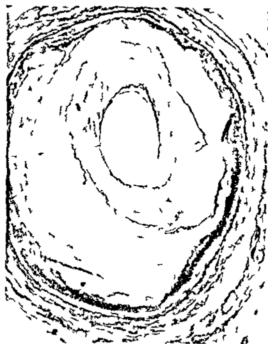


Fig 17

Con cntri th kening of nti ia due to ove lapping of deposits L A D B Case 16 Sh idi i 30



Fig 18

Irregula layeri g caus ng signet ri g deformity R Cor Case o Sh rid n × o



Fig 19

Recent depos t sta ning l ke collagen superimposed on older denser d pos t R Cor Case 34 Sherida i × 30



Fig 20

Elastosis extending beyond base of plaque It i penetrated by a large vas L A D B Case 28 Sherid × 110

XX

The Episodic Nature of Intimal Deposits

In the first few hundred sections examined the differential stains revealed bewildering contrasts of a variety unsuspected in the haematoxylin-eosin preparations but later it became possible to disentangle the various elements and to recognize certain patterns that tended to recur throughout the series

One of the earliest impressions gained was that coronary atherosclerosis is not merely a progressive disease but that it progresses in a series of episodes rather than gradually This is in accordance with Duguid s view that severe narrowing is the result of recurrent thrombosis The subsequent findings in the present investigation all tended to support this contention It should be re-emphasized however that this study has largely been confined to the more severe degrees of atherosclerosis

A rough grading of the severity of coronary narrowing has been made by *White et al* (1950) in which they recognize four degrees (*a*) Slight diffuse thickening of the intima (*b*) Concentric thickening of the intima up to a thickness of two or three times greater than that of the media (*c*) Signet-ring atheroma narrowing the lumen to about half its original width (*d*) Subtotal occlusion in which the intima is reduced to a tiny slit to one side of the vessel

It will be seen from the subsequent photomicrographs that the majority of the series were on grades (*c*) and (*d*) For comparison the wall of a normal coronary artery is shown in Fig 15

Before considering the evidence for the episodic nature of coronary atherosclerosis an argument to the contrary may be quoted From a study of 536 hearts with coronary disease *Lober* (1953) has demonstrated a steady parallelism from youth onwards between the subject s age and the degree of coronary sclerosis This merely confirms what was already known namely that atherosclerosis increases with age and it is difficult to see why Lober and his supporters should claim that this work disproves the *episodic* nature of the disease Whether atherosclerosis be episodic or gradual due to recurrent thrombosis or gradual lipid accumulation there will still be a correlation between the age of the subject and the degree of intimal thickening

A LAYERING

In haematoxylin-eosin sections the intimal thickening may be signet ring or concentric in type according to whether the lumen is eccentrically placed or not However selective staining of the elastic tissue reveals that there is no essential difference in the nature of the deposits both showing the phenomenon of recurrent layering In signet-ring deformities the serial layers are set one on top of the other (Fig 16) whereas in concentric

narrowing a series of roughly crescentic deposits overlap (Fig 17) giving the impression that the roundness of the lumen has been preserved by the force of the blood-stream Fig 18 shows how a signet-ring deformity may also be produced by irregularly overlapping deposits

Each layer consists basically of a network of coarse fibres with the tinctorial reactions of collagen with few cells and a meagre blood-supply The most recent deposit is usually less dense than its predecessor (Fig 19) Superadded features are foci of haemorrhage old or recent and various forms of degeneration and necrosis lipid accumulations or plaques of calcification

B INCREASED ELASTIC

An increase in the amount of intimal elastic is a prominent feature in coronary occlusion and takes three forms (1) Multiplication of the internal elastic lamina (2) A covering of the serial deposits by fine elastic membranes (3) Elastic envelopment of the blood-spaces in a recanalizing thrombus

(1) MULTIPLICATION* OF THE INTERNAL ELASTIC LAMINA

Jores (1898) observed a hypertrophy of the intimal elastic of arteries which increases with age He did not regard this as the result merely of physiological ageing however but as a pathological process due to increased strain *Thayer and Fabyan* (1907) showed that reduplication of the internal elastic lamina can be seen in the radial arteries of healthy children and by the third decade is a constant feature Since it may occur in the absence *of atherosclerosis or hypertension they believed the elastic changes signified wear and* tear of ageing arteries rather than a specific disease Others have claimed that elastic reduplication is not a primary change but is preceded by degenerative lesions in the intima both in the human subject (*Klotz* 1915a) and experimental animals (*Saltykow* 1908) Whether the phenomenon be degenerative or regenerative in origin the term elastosis will be used in this text in the interest of brevity to signify the increased layers of intimal elastic that frequently lie at the base of atherosclerotic plaques (Fig 22)

It has now been shown that the coronary arteries of healthy infants show reduplication of the internal elastic lamina soon after birth (*Gross et al* 1934) At an early age longitudinal muscle fibres proliferate to form the *musculo-elastic layer* and the inner elastic membrane continues to split off finer layers to form the *elastic hyperplastic layer* a process that increases with age Fibrosis calcification and lipid deposits are regarded by Gross as late secondary phenomena the whole process being the inevitable result of ageing

Gross's observations were made on individuals who had not died of cardiovascular disease The relation of age to atherosclerosis is discussed in Chapter IX at this stage one may observe that attempts to separate the physiological from the pathological in the age-process have not only been unsuccessful but have led to confusion

Many others have looked on this fibro-elastic thickening of the intima as an indication of that intimal damage which predisposes to lipid infiltration and atherosclerosis It is

* The term is used in the sense of an increased number of fibres without implying active *proliferation* since little is known of the way in *which elastic tissue is formed*



Fig 21

Elasto s showing d scontinu ty and poor taining quality of new fibres L A D B Case 32 Sheridan × 75

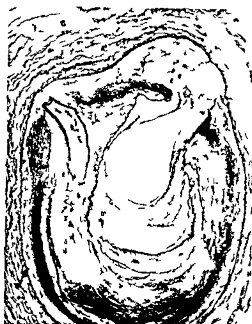


Fig 22

Thick layer of elasto is between media and vascular crescent (e pre eding pl que formation) L A D B Case 16 Sherid n × 35



Fig 23

Se al l t c layers continuous with ela ti at marg s of pl qu nd fading off towards centre of plaque R. Co C e 18 Sheridan × 45



Fig 24

Deposit ro d mo h of b ch artery show g layering nd co tinu ty fel t em mbranes with elastic of br ch. L.A.D B Case 30 Sherida × 15

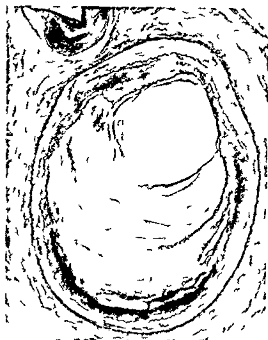


Fig 5

Serial elastic laminae ontinuous with elast at margins of plaque defecti e ne r centre Considerable el stosis. L A D B C se 16 Sheridan × 35

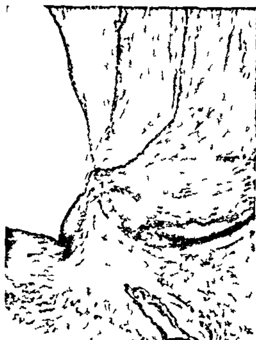


Fig 26

Ma g n of pl que showi g serial elasti laminae on tinuou with internal lamin of ve sel R Co Case 29 Sherid n × 40



Fig -7

Buried elastic probably distorted by rupture due to haemorrhage R. Cor Case 9 Sheridan × 45

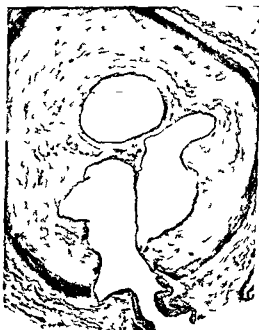


Fig 28

Recanalized thrombus showing elastic lin ng blood spaces continuous with elastic of branch vessel R. Cor Case 15 Sheridan × 40

certainly a fairly regular feature of atherosclerotic vessels but the extent of the elastosis is not confined to the area of the plaque (Fig 20) The finer fibrils between the main layers lack the continuity and sharp affinity for orcein that characterize the healthy lamina (Fig 21) and it may be that these are either an immature or a debased form of the thicker membranes In some plaques a broad layer of elastosis at their base is a prominent feature (Fig 22)

(2) COVERING OF SERIAL DEPOSITS

In the substance of the plaque itself are fine elastic membranes sharply demarcating the serial deposits and continuous with the elastic at the margins of the plaque (Fig 23) or with the healthy intima of a branch artery (Fig 24) The central part of the membrane may be defective (Fig 25) as though a fresh deposit had occurred before the elastic coating of the old one was complete

As the recurrent deposits become thicker a phenomenon already referred to as layering their elastic integuments are more widely spaced and in advanced accumulative lesions the serial layers of elastic may be clearly preserved (Fig 26) Fragmentation or distortion of the layers such as appear in Fig 27 are unusual and probably due to secondary degeneration or haemorrhage in the plaque

The resistant nature of elastic tissue is notorious and it is the last formed element to disappear in necrotic lesions like infarcts or gummata The importance of this observation lies in the fact that an elastic membrane deeply situated in a sclerotic plaque could act as a barrier to the ingrowth of nutritive vessels from the media The continuous elastic membrane also appears to prevent firm union between the collagenous surfaces on either side of it so affording a natural plane of fission between deposits when the plaque is disrupted by haemorrhage This occurrence is dealt with in Chapter XXIV under Dissection The purpose of the newly formed elastic can only be guessed at but it does seem to form a protective covering for the diseased and porous intima a basis for a new endothelial lining and a buttress against the blood-flow at arterial pressure

(3) ELASTIC TISSUE IN CANALIZED THROMBI

A similar phenomenon is observed in the course of recanalization of a thrombus where the elastic can be traced from the intima of a branch to the lining of blood-spaces formed by retraction of the clot (Fig 28) It would appear that whenever blood takes a new course elastic tissue forms a protective wall around it and that when a new blood channel is formed an effective elastic membrane in its wall is a condition of its permanence

Irregularly disposed elastic may also be seen in the heart of an organizing thrombus ensheathing the newly formed blood channels (Fig 29) and both elastic and blood channels can be traced in serial sections either to the lumen at one or other end of the thrombus or more frequently to the mouth of a branch artery

It is of interest to note that young elastic tissue stains vividly in PAS preparations apparently before it has acquired an affinity for orcein (Figs 30 31)

C SMOOTH MUSCLE PROLIFERATION

The apparently reparative qualities of elastic tissue are equalled in extent if not in frequency by smooth muscle which proliferates freely in atherosclerotic plaques or segments occluded by organized thrombosis This is a phenomenon liable to be overlooked in haematoxylin-eosin preparations though it shows up readily enough in sections stained by PTAH or Azan

Muscle-fibres in plaques can usually be traced to one or other of the following (1) The media at the margin of a plaque (Fig 32) (2) The longitudinal fibres of the musculo-elastic layer (Fig 33) (3) The media surrounding the mouth of a branch vessel (Fig 34)

In one instance muscle fibres appear to have grown directly into the plaque from the media at its base (Fig 35)

The new muscle usually lies just below the lining of the narrowed lumen sometimes completely encircling it and apparently serving no useful function (Fig 36) Similarly in organizing thrombi muscular ingrowth as with the elastic can be traced to the vessel wall at either end of the clot (Fig 37) or from the mouth of a branch vessel (Figs 38 39) encircling either the blood-spaces formed by retraction of the clot or the small channels supplying it although only a minority of the latter may be so favoured (Fig 40) As with the elastic growth may be rather irregular or excessive On one occasion a substantial cylinder of new muscle had formed round the vascular channels running through the heart of an organized thrombus completely surrounded by a thick layer of atherosclerosis (Fig 41)

The similarity in distribution between new muscle and elastic tissue suggests a similar rationale namely the provision of elements required to furnish a new artery wall irrespective of whether they can function effectively or not The significance and origin of smooth muscle fibres in early intimal thickening have been considered at length by *Altschul* (1950) Finally the tendency for elastic tissue and smooth muscle to occur both in atherosclerotic plaques and in organizing thrombi should not go unnoticed by protagonists of the thrombogenic theory



FIG)
El stic irreg l rly she thing blo d-sp n recanal d th ombus R Co Case 7 Sheridan × 45



FIG 30
El t c like ti su t ng ly PAS po ti e in o g nizi o thrombus (f F g 31) R Co C se 10 PAS 30



FIG 31
Th same show g bsence of ff nity of ela tic like tiss f r re orci Sheridan × 30



FIG 32
Muscle grow g into plaque f om med at its margin where elastic lam na is defect e L A D B Case 11 PTAH × 60



Fig 33
Muscle app rently arising f om f bres internal to inner elastı la una (seen as a white w vy line) L A D B Case 8 PTAH 45



Fig 34
Muscle at margin of plaq e directly ontinuous w th *medı of b anch essel R Cor Case 35 PTAH × 35*

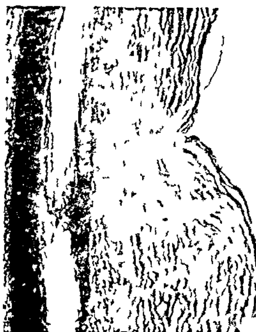


Fig 35
Proliferating *muscle deep in plaque* linked with *media by* growth round a nutrient capillary L A D B Case 23 *PTAH × 85*



Fig 36
Complete encirclement of na rowed lumen by muscle f bres. L Circum flex Case 15 PTAH × 60

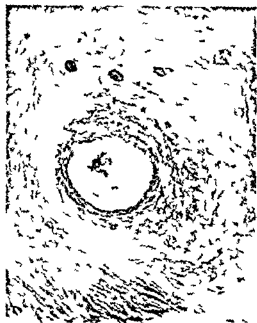


Fig 37

Org nized thrombus w th new blood-ch nnel surrounded by non-functioning sm oth muscle L Circu flex Case 3 PTAH × 30

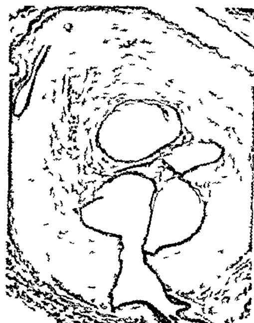


Fig 38

Muscl grow ng into r c n lized thrombus from n ed a of br nch rt ry (cf Fig 39) R Cor C se 15 PTAH × 40



Fig 39

Th same H gher magnif cation of adj cent section showing muscle in septum between blood paces PTAH × 75



Fig 40

Org nizing thrombus showing muscle round one blood-pace nly R Cor Case 10 PTAH × 45

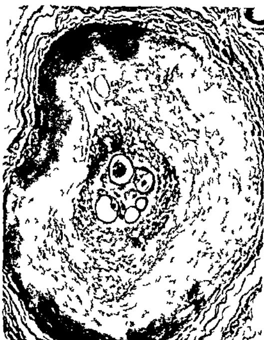


FIG 41

Cylinder of muscle urrounding blood-chann ls in centre of recanaliz d thromb s R Cor Case 7 PTAH × 35



FIG 42

Superf cial and deep f brosis w th itermedi te zone of degeneration R Cor Case 25 Sherid n × 35



FIG 43

Vessel penetrating media to link up with periphe al blood sinuses t base of plaque R. Cor Case 25 PAS × 75



FIG 44

Large v s tra ers g m dia to join blood s ju es t b se of pl que L A D B Case 16 Azan × 40

XXI

The Role of Intimal Vascularization and Haemorrhage

INTIMAL VASCULARIZATION

MORE important in the evolution of coronary atherosclerosis though perhaps less spectacular is the proliferation of capillaries throughout the plaque To comprehend what follows a brief consideration of the earlier literature is necessary

The intima of healthy human arteries as stated previously is nourished by direct imbibition from the blood in the lumen and is not supplied by the vasa vasorum (*Woodruff* 1926 *Robertson* 1929) In atherosclerosis however the bulk of the plaque renders some degree of vascularization necessary if nutrition is to be maintained

Vascularization of the intima in arterial disease was known to *Rokitansky* long ago (1841-46) until recently however its role in the pathogenesis of coronary occlusion was overlooked *Wolkoff* (1929) described a plexus of small vessels in atherosclerotic patches derived from the vasa vasorum and from capillaries communicating directly with the main lumen but she regarded its function as connected solely with the resorption of lipid from degenerate plaques and not as an important factor in the evolution of the lesions Similarly *Leary* (1935a) stated The influence of the vasa vasorum in connection with the lesions of atherosclerosis is relatively unimportant

However *Paterson* (1936) found that haemorrhage from the capillaries in atherosclerotic plaques was a frequent source of coronary thrombosis He attributed a nutritive function to the vessels the plexus derived from the vasa supplying the deeper part of the plaque the superficial network arising from the lining endothelium to subserve the top layer These two plexuses communicated but as some of the vessels lay in degenerate areas they were liable to be ill-supported and certain of them communicating with the main lumen at arterial pressure were prone to rupture In a later paper (1938) he maintained that secondary thrombosis in the lumen could result from (1) Superficial haemorrhage causing diffusion of a thromboplastic substance from the intima to the lumen (2) Rupture of nutrient capillaries leading to necrosis of the overlying intimal lining (3) Retrograde thrombosis from a ruptured capillary in the direction of the lumen

Wartman (1938) showed that a larger haematoma in the depths of the plaque could cause fatal occlusion merely by raising the overlying intima and compressing the lumen to a narrow slit *Winternitz* and his associates (1938) by employing the Spalteholz technique on diseased arterial segments were able to confirm the existence of the two communicating vascular networks but the value of their work was somewhat marred by their arguments (1) that the healthy intima has a capillary blood supply (a claim they were unable to substantiate) and (2) that atherosclerosis is no more than the end-result of repeated intimal haemorrhages a theory that brought a reminder from *Leary* (1938)

that atheroma begins in the most superficial layers of the intima in the part furthest removed from the vasa

Following *Duguid's* theory of the thrombotic origin of atherosclerosis earlier beliefs were somewhat modified *Geiringer* (1951a) developing Paterson's concept maintained that *vascularization is a function of intimal thickness* and that when the coronary intima exceeds the critical thickness of 0 35 mm nutrition by imbibition from the lumen is no longer adequate and vessels grow into the plaque to nourish it The deeper layers are supplied by transmedial ingrowth from the adventitial plexus the superficial zone by vessels derived from the organizing thrombus which (by Duguid's postulate) is the basis of the plaque These two plexuses may anastomose but should the superficial one be lacking the plaque is sustained by the vasa alone and necrosis of the central part may follow

Crawford and Levene (1952) have advanced the theory that the superficial plexus is derived from the endothelium of the lumen which overgrows the clot from its margins They believe that endothelial cells are also capable of assuming the function of fibroblasts and help to organize the superficial part of the thrombus The superficial and deep organizing processes may fail to link and the residue of the clot deprived of blood may undergo fatty degeneration and necrosis This would account for the appearance of Fig 42 *in which the degenerate zone is sandwiched between inner and outer rings of fibrosis* a not uncommon phenomenon

The present investigation carries these arguments a stage further The concept of superficial and deep vascularization is sustained with certain modifications set forth below

The deep plexus

Reference has been made to the gaps in the media caused by the passage of hypertrophied vasa vasorum On entering the base of the plaque these often link up with a series of peripheral blood sinuses (Fig 43) The latter though thin-walled are not capillaries in the ordinary sense being much larger and often irregularly shaped Crescents of these sinuses are seen between the media and the base of the plaque (Fig 44) and this distribution is so striking that it is difficult to escape the conclusion that they are the late result of retraction of the thrombus from the vessel wall – i e marginal recanalization Their mode of origin in a recently thrombosed artery is suggested by Fig 45

This belief is strengthened by a study of plaques showing layering When a second thrombus is deposited on the first a crescent of vessels derived from the endothelium covering the first thrombus may be formed between the deposits (Fig 46) If there are several deposits the vascular crescents may be found to be closely related to the elastic membranes separating them (Figs 47 48)

The superficial plexus

This too would seem to be primarily a by-product of thrombosis rather than a purposeful attempt to nourish the superficial layers of the plaque – which are in any case already nourished by imbibition from the lumen As organization proceeds the blood-

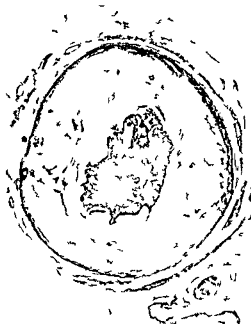


FIG 45
I terrupt d iarg l t tion f recent th o nbus show ig how periph l bl od p es may originate L A D B (C se n t n series) H E × 20



FIG 46
Re ent th o b e f br us pl q e th marginal c l r on a d g owth f nd th l round blo d sinus s R Co C 33 H E × 75

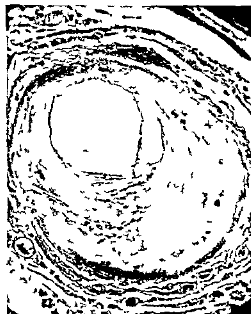


FIG 47
S gnet g defo ty w th se l cr ce ts of sel (cf F g 48) L A D B C se 16 PTAH × 25

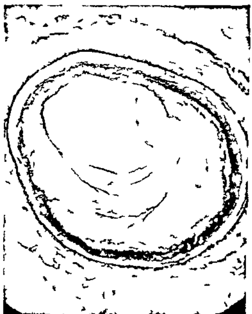


FIG 48
The e show g how vessels run between se l deposits (den cated by elastic membranes) She dan × 25



Fic 49

Org uz ng thr mbus ith large blood si ses li ked to lumen ia pit on surfa e of depo it R Cor Case 5 Sh rid n × 75



Fig 50

Sm ll vessel communicat ng w th lumen Se ial section rev al unio i w th plexus seen deep r in plaque L A D B Ca e 4 PAS × 160

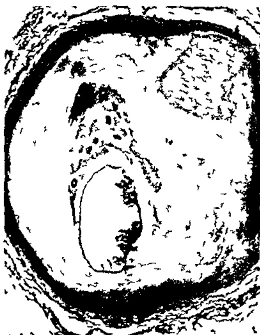


Fig 51

Organizing deposit showing angul vessels w th mar ginal and deep haemorrh ges R Cor Case 33 PTAH × 25

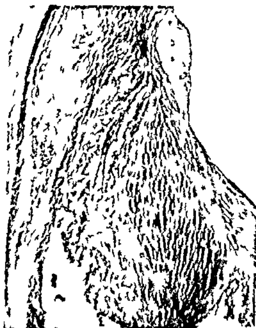


Fig 52

Thin-walled vessel ran ifying in margin of degenera e zone L Circumfl x Case 13 PAS × 40

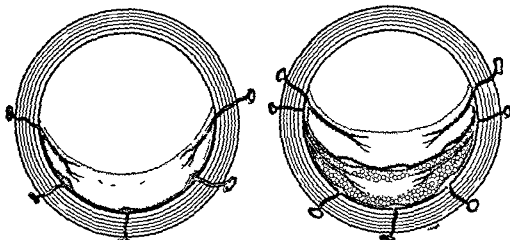


Fig 53
Diagrammatic representation of va ularization of a ngle depos t (left) and a depo it com posed of two l ers (i ht)



Fig 54
Thi walled ll-suppo t d a cular twigs in degenerate p rt of plaq e L A D B Case 28 PAS × 85



Fig 55
O g-n zing thrombus showing ingrowth of endoth l um from lumen to line a blood-sinus L Cor Case 9 H E × 125



Fig 56

Pitting of surface (top left) at po nt whe e vessel in plaque communicate with lumen L Cir umflex Case 21 Azan × 40



Fig 57

Blood-spaces between ser al depo it comn t ng vith lumen thro gh large rregul r opening t on m gm R Cor C se 2 Azan × 35



Fig 58

Capill ries pa sing f om branch artery into plaque ur rounding n outh of branch R Cor Case 33 PTAH × 30



Fig 59

Fibrino d necrosis of an arteriole in f brous pl q e of a hyperten ive d betic subject R Cor C se 25 PAS × 251

spaces are reduced in size and number (Fig 49) until a network is left which is adequate for the supply of the plaque

Once organization is complete however there is no reason to suppose that the superficial plexus continues to derive blood from the lumen as some have maintained Indeed all the evidence indicates that while communications with the lumen undoubtedly occur (Fig 50) they are sufficiently scarce even in serial sections to be wholly inadequate for *the maintenance of an effective blood-supply Free communication however can readily* be demonstrated between the superficial and deep plexuses and it is thus likely that when organization is completed the extent and distribution of the vascular network is thereafter determined by the requirements of the plaque only and that the united plexuses function as one supplied by the enlarged vasa vasorum

Angular vessels

Besides being nourished from its base the plaque very frequently receives a blood-supply from fairly prominent vessels which enter it from the margins These angular vessels are a highly characteristic feature of degenerate plaques and are a prime source of haemorrhage (Fig 51) They can be traced by serial sections into the atheromatous focus (Fig 52) and in the other direction they communicate with the vasa vasorum Being primarily concerned with scavenging they ramify in the degenerate areas where they are thin-walled and poorly buttressed (Fig 54) and so are liable to rupture causing haemorrhage into the softened area

Their presence in degenerate foci was taken by *Leary* (1936a) to negative any claim that the vessels supplied nutrition to the plaque but there is good reason to suppose that the degeneration occurred first and that the vascular twigs in such areas are a response to the need for absorption of necrotic tissue If this is true it is an observation of some importance and the subject is discussed later under Degeneration in the plaque

In gross signet-ring deformities with several superimposed deposits a whole series of these vessels may form a prominent plexus at the margins of the plaque Branches are given off to each layer and if atheromatous softening is a feature micro-haemorrhages are common (Fig 7)

The vasculature of the plaque as described up to this point is shown diagrammatically in Fig 53

Communication with the lumen

This is so infrequent that it may be regarded as both incidental and insignificant Ingrowth of capillary endothelium from the lumen may occur in recent thrombosis as shown in Fig 55 and as suggested by Crawford and Levene but this seems to be a feature of organization and not a provision for the nutrition of the plaque later on

Occasionally a small pit can be observed in the surface of the plaque communicating with a superficial network One of these has been shown in an organizing thrombus (Fig 49) and others were seen in fibrous plaques (Figs 56) Their mode of formation is suggested by Fig 57 which shows a partially organized thrombus on the deep aspect of

which are several large blood sinuses communicating with the lumen through a large opening *Paterson (1936) was first inclined to think that communication with the arterial* blood in the lumen was a factor in causing rupture of the capillaries in the plaque but later (1938) he revised this view and stated that lack of support by the degenerate lipid was the most important consideration

Miscellaneous observations

A bizarre appearance noted on several occasions was caused by several small vessels *passing into the plaque on either side of a narrowed lumen* close to the mouth of a branch artery (Fig 58) A similar picture is illustrated on pp 25-6 in the monograph of *Wintermitz et al* (1938) attributed by them to the passage of vasa vasorum from the branch vessel Comparison with Fig 24 however shows that they are simply a part of the deep vascular network that forms between serial deposits – in this case round the mouth of a branch artery In fact one of the twigs terminates in a zone of necrosis

Fibrinoid necrosis of an arteriole in the centre of a plaque was observed only once (Fig 59) *in a diabetic patient with hypertension*

The conclusions reached on the subject of intimal vascularization may be briefly summarized (1) The deeper parts of the plaque are supplied by peripheral vascular clefts which form as a result of marginal retraction of the clot and later link up transmedially with the hypertrophied vasa vasorum (2) The superficial vessels are the residue of organization of a mural thrombus ultimately deriving their blood-supply from the deep plexus and not from the main lumen (3) When organization is complete the subsequent extension of the vascular network is determined by the dual requirements of nutrition and degeneration (4) This network though readily demonstrated is inefficient and inadequate for these requirements and so degeneration and haemorrhage occur in the plaque and their waste-products accumulate therein

HAEMORRHAGE IN THE PLAQUE

Once an atherosclerotic plaque has undergone degeneration small haemorrhages into the softened area from the ill-supported vessels at its margins are an almost constant feature These extravasations are no mere terminal event and the frequency with which they occur is indicated by the presence of several small haemorrhages in a single deposit *clearly of different age though all recent enough to be identifiable microscopically* (Fig 51) It is therefore safe to assume that the average atheromatous abscess has been subjected to repeated micro-haemorrhages over a long period and that its pultaceous contents are partly haemic in origin

When blood is discharged into a degenerate focus it disrupts the contents and becomes intimately mixed with them (Figs 60 61) When the haemorrhages are multiple and of different ages it becomes difficult to distinguish atheromatous softening from altered blood although staining by Azan and PTAH assists in differentiating some of the elements Fig 62 shows a typical atheromatous abscess in which macrophages with foamy cytoplasm



F c 60

Re ent h n o thage n athero tou f us R d lls f b m l p d cry tals and amo phou p e are n ungl d R Cor C se 5 Ar 45



F 61

R ent h e hag l p d fo u F lls a e u t ly e d ith bl d L A D B C se 30 H E 75



Fi 62

Atheron tous bsce w th recurr h o has Red lls a e mingl d w th f am lls d lb no d br nd (b tt ght) f brin n tw rk I Co Case 4 A n 5



F 63

Congest d but th n-w ll d essel poorly b sed by surr u d g d gen te m terial L C cumfl x Case 32 A an × 135

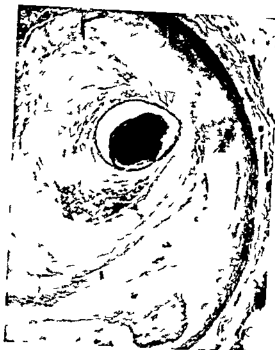


Fig 64

Angular haemorrhage in organizing depos t in turn surrounded by gross fibrous thickening L A D B Case 28 Azan × 30



Fig 65

M ssive recent haemor hage i to atherot atous bscess L A D B Case 4 Azan × 20



Fig 66

Recent haemorrhage into plaque reducing lumen to a narrow slit L A D B Case 17 H.E × o

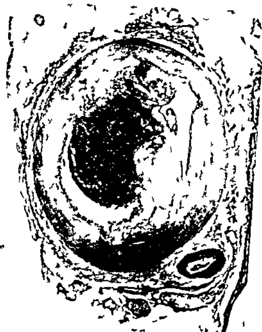


Fig 67

Recent h emorrhage into plaq e leaking through int ma and initiating a sm ll polypoid thrombus L A D B (Case not in series) H E × 20

eosinophilic granular proteinous debris recently extravasated red cells and a coarse fibrillar network of degenerating fibrin are all recognizable In fact every possible combination of degenerative and haemic elements was observed throughout this series with every possible transition between atheromatous softening and altered blood The wide range of appearances can be satisfactorily accounted for only on the assumption that they represent the degenerative products of haemorrhage as well as necrosis Therefore Duguid s hypothesis that atheroma is a process of fatty degeneration occurring in a thrombus should be extended to include the residues of intimal haemorrhage

It may be objected that this is not the manner in which haemorrhage or thrombosis are dealt with in other tissues but consideration must be given to the fact that the atheromatous abscess owes its presence to inadequate vascularity of the plaque and the resistance of cholesterol to absorption Thus the usual features of haemic organization – i e granulation tissue phagocytosis of haemosiderin etc – are not generally observed

In *veins* the conditions preceding thrombosis are very different since the intima on which the clot is deposited is usually a healthy vascularized membrane which allows rapid ingrowth of capillaries into the thrombus followed by the customary features of organization But in atherosclerotic arteries the intima has been replaced by a thick relatively avascular plaque and quite large thrombi may become sealed off from the rest of the circulation by a fibrous cylinder and ultimately degenerate into a yellow pultaceous fluid with a high lipid content This process is not confined to coronary arteries and may be seen in long-occluded arteriosclerotic aneurysms (Fig 3)

The factors producing intimal haemorrhage have been fully reviewed by *Paterson* (1936 1938) the main ones being the thinness of the vessel wall in relation to its diameter and the lack of support afforded by the surrounding degenerate material in the resorption of which the vessel is engaged (Fig 63) The *extent* of the haemorrhage is determined by *the nature of the supporting tissue in the reticular network of granulation tissue it is* generally quite small (Fig 64) whereas in soft pultaceous foci it may be massive (Fig 65)

Larger haemorrhages are readily visible to the naked eye varying from red to brown according to their age The *track* of such haemorrhages is also determined by morphological considerations Dense collagen acts as a barrier and in a deeply placed focus of softening the blood may be confined and converted into a haematoma which swells the plaque and narrows the lumen further (Fig 6)

In the more superficially placed foci however the blood tracks towards the lumen and causes occlusion or sudden death (1) By raising the overlying intima and compressing the lumen into a narrow slit at one side of the vessel (Fig 66) In the autopsy room this is often mistaken for a clot occluding the lumen (2) By damaging the intima by leakage (Fig 67) so initiating secondary thrombosis in the lumen (3) By eroding the roof of an atheromatous abscess causing rupture of its contents into the lumen followed by secondary thrombosis (Fig 68)

A deep haemorrhage may track obliquely towards the lumen between two serial deposits and emerge at the margin giving rise to thrombosis or even rupture of the plaque (Fig 140) This phenomenon is considered later under the heading Dissection and seems to

be due to the existence of a natural plane of fission between the deposits I believe that this is because they are separated by an elastic membrane which prevents firm union of the collagen on either side (Fig 138)

Small subendothelial haemorrhages are common too raising the endothelium and its basement membrane from the underlying plaque They are frequently observed to occur at the margin of a superficial layer of lipid-containing macrophages (Fig 69) where as in the deeper foci marginal vascularization occurs The importance of the superficial haemorrhages lies in their capacity to initiate thrombosis

Summarizing one may say that the *small* haemorrhages are important because of the cumulative effect of their degenerative products while the *larger* ones are important because they may cause occlusion or initiate thrombosis Their ability to compress the lumen against arterial pressure has been questioned (*English and Willius* 1943) and *Drury* (1954) has stated that all the larger haemorrhages are due to irruption of blood from the lumen through a tear in the plaque His experience is in direct opposition to the serial-section studies of *Paterson* (1936) *Wartman* (1938) and myself

Fig 67 for example shows a recent haemorrhage in a deeply placed atheromatous abscess Blood has leaked through the roof of the plaque and has caused a small thrombus to form on the devitalized lining of the vessel shortly before death It is difficult to see how this could have resulted from irruption of blood from the lumen



Fig 68

Rupture of thero tous b s ı t l m c using th ombos s L A D B C se 34 I TAH × 25



Fig 69

Sm llh e h q f o n gınal ssel b d›thelıal l pıd depo ıt overlyı g f b o pl q L Cı cu fl × C se 13 H E × 45

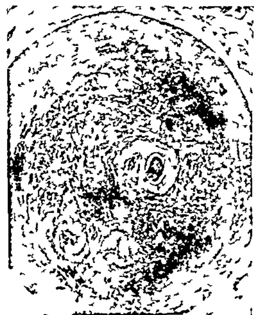


Fig 70

Sl ghtly atherosclerotic artery t tally oc l d d by o g zıng th o b s, rich ın vessel c ll d haemo derın (exc pt n l) L A D B Case 40 H E × 30

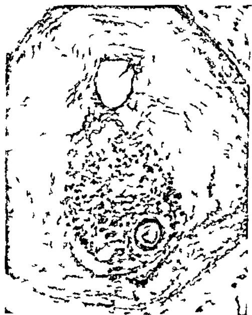


Fig 71

O ganızıng thrombus ın essel lre dy grossly n rrow d by f brous atherosclerosı R Co Case 10 H E × 30

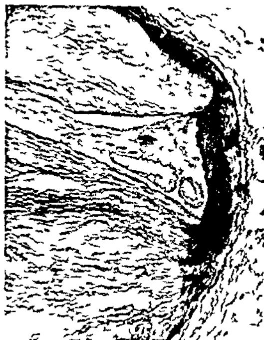


FIG 72

Narrow bai d of granulation tissue in gro corona y oc lusion showing vascul r base der ved from healthy segm nt c f vessel w ll L C u nfl x Case 13 Sherida 1 40



FIG 73

Atypic l gr nul tion ti ue oft n fou d long w th gro s intin al fibro is L A D B Case 9 H E × 40

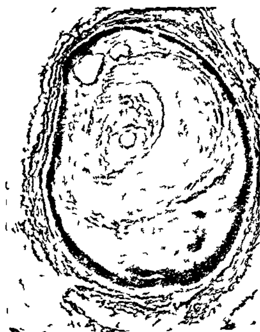


FIG 74

Subto al *occlusion by 3 success ve deposits* all densely fibrous and avascula L A D B Case 32 Sheridan × 35

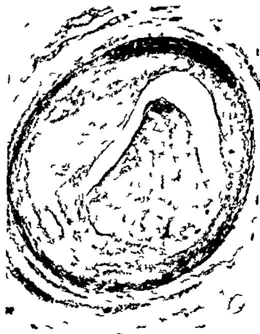


FIG 75

Re ent thrombu retra t ng to allow ma ginal reca aliza tion at one s de L A D B Case 34 Azan × 30

XXII

The Nature of Arterial Thrombosis

MOST of our concepts of the morphology of intravascular thrombosis and recanalization are based on a study of diseased *veins* But the circumstances under which arterial thrombosis occurs are rather different especially if the artery is atherosclerotic For one thing there is the force of the blood-stream at arterial pressure tending to mould the surface of the clot and to dislodge the looser elements Secondly there is the avascular state of the intima exaggerated in atherosclerosis and forming a poor basis for organization as compared with the vascularity of its venous counterpart Thirdly there is the difference in oxygen tension in venous thrombosis the low oxygen tension is a stimulus to capillary growth whereas in arteries both the higher oxygen tension and the greater hydrostatic pressure impede the growth of young vessels (*Crawford and Levene* 1952)

Again the venous system is a network and when one passage is obstructed the blood fairly easily finds an alternative route When an artery is blocked however infarction occurs unless the circulation is maintained by (a) recanalization or (b) collateral circulation

Early in the present investigation the differences between arterial and venous thrombosis and their sequelae became apparent Complete occlusion of the lumen by granulation tissue alone similar to that seen in organization of a venous thrombus is on the whole exceptional in coronary atherosclerosis (Fig 70) although lesser degrees are common enough e g in the final closure of a vessel already severely narrowed (Fig 71)

In such instances the granulation tissue contrasts sharply with the acellular plaque and its basis can always be traced to a segment in which the intima has escaped severe thickening An extreme example of this is illustrated in Fig 72 Even the granulation tissue may be atypical with the usual capillaries and reticulin network but few fibroblasts or leucocytes and little sign of a vascular communication with the surrounding plaque (Fig 73)

A reasonable inference is that healthy granulation tissue demands an ample vascular supply and this is lacking on the surface of an atherosclerotic plaque But if this is so how do the crescentic and relatively avascular serial deposits come to be organized one on top of the other even to the point of occluding the vessel (Fig 74) If we believe that they originate in thrombi there must be something different either in the manner of their formation or their organization – or both

Two other anomalies demand explanation Firstly there is surprisingly little evidence of red cell destruction in the form of haemosiderin in young atherosclerotic plaques although it is a prominent feature of organizing venous thrombi Secondly despite the frequency of superimposed deposits there is little sign of intermediate stages between whole blood and collagen recent deposits apparently having a coarsely laminated structure at an early stage

After examining a considerable number of plaques and thrombi of all types I have come to the conclusion that such atherosclerotic plaques originate in this manner following thrombosis the majority of the red cells are washed out of the fibrin network by the force of the blood-stream which moulds the fibrin into a pale laminated crescent to one side of the vessel and that thereafter organization is effected by fibroblastic ingrowth from the surface transforming the fibrinous laminae to collagen without the aid of extensive capillary proliferation

The germ of this hypothesis is not new *Rokitansky* (1841-46) wrote The deposit is an endogenous product derived from the blood and for the most part from the fibrin of the arterial blood *Duguid* (1949) stated that most arterial thrombi do not cause total occlusion but merely form fibrinous deposits on the intimal surface *McLetchie* (1952) noted that mural thrombi induced in the pulmonary arteries of experimental animals by injections of Russell viper venom rapidly became pale and concluded that the haemoglobin had been washed out of them *Crawford and Levene* (1952) suggested that fibrinous laminae could be converted to collagen by endothelial cells growing in from the surface and assuming the function of fibroblasts

Fig 75 shows a recent thrombus retracting from the vessel wall to permit a certain *amount of marginal recanalization A higher magnification (Fig 76) shows it to contain* a number of irregularly shaped lakes of red cells and leucocytes lined by fine membranes not unlike the lines on a contour map and tinctorially equivalent to fibrin * It will be noted that the proportion of fibrin to cells is unusually high As the fibrin continues to retract the cells will be squeezed from the interstices assisted by a blood flow at arterial pressure

RECANALIZATION

As a rule the clot is attached to the vessel wall on one side only and becomes flattened *towards its base by the pressure of the arterial blood* the fibrin network being compressed into a series of laminae parallel to the vessel wall rather like the layers in an aneurysmal sac (Figs 77 78) Most of the red cells are washed away but the remainder coagulate between the fibrinous laminae and come to form part of the deposit The whole thrombus soon loses the staining properties of fibrin and red cells (Fig 79) and in haematoxylin-eosin sections comes to resemble hyalinized collagen a fact also noted by Duguid (1948 1955)

At an early stage the retracting surface becomes overgrown by the luminal endothelium at the margins a phenomenon that seems to occur fairly rapidly (Fig 80) Elastic overgrowth also occurs and the superficial layers of the clot are organized from the surface (Fig 81) possibly in the manner suggested by *Crawford and Levene* (1952) The deeper part is organized by means of the plexus which forms between vessel wall and deposits and if this is inadequate degeneration follows

Retraction of the clot is a major factor in restoring blood flow and preventing myocardial infarction It thus occurs early before the constituents of the clot have lost their staining

* My colleague Dr J H Humble of the Haematology Department of Westminster Hospital has suggested that these lakes in the fibrin may be due to the action of fibrinolysin elaborated by the leucocytes in them



FIG 6

The st ne ı gen f d to ho fib in net o ker l l k of d ll nd leu cyt PAS ı2



FIG 7

R t th bu t t n t wa d base F b n two k t ndı to b o ı p sd nto p ll l l y R ((u) PTAH 30



FIG 78

Old part f same th ombu f btin comp essed int l n n p ll l u th b se of l t PTAH 30



FIG 79

Oldest p rt of sam th o bus base show ı los of t ning p opernes of f b n and onglutinat d red cells PTAH × 30

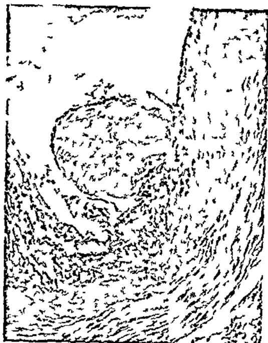


Fig 80

Recent mu al thrombus (fib n still etained affi ity for PTAH) lready o e grown by lining endothelium L Circumflex Case 25 H E 135



Fig 81

Depos t undergoing organi ation fro n s i fac L A D B Case 28 H E × 125

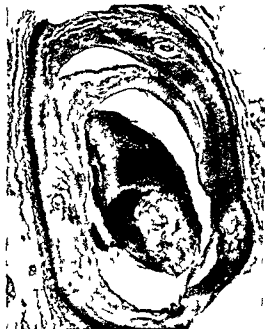


Fig 8

Retraction of thrombus has caused older deposits to be pulled away from deepest depos t in 2 places L A D B Case 30 PTAH × 20



Fig 83

Contracted orga ized thrombus causing wrinklin of older depos t outside it F brin has oozed into terven ng cleft L A D B Case 34 PTAH × 45



Fig. 84

Reca al zat on effect d by la ge blood paces in tre of lot Note da kly sta ning f b in sept b tween sp R Cor C e 25 PTAH × 40



Fig 85

Ag ng f b n us n twork in l en nd hae n t ma in pl que be eath Both h v lost ff ty f PTAH L A D B C 31 PTAH × 35

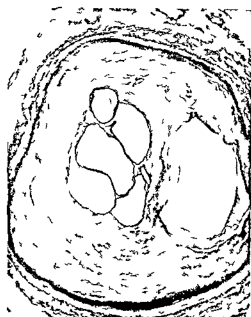


Fig 86

T ile d f o g zed th n bu conta ing lt ple bl d-sp ce (These co le c wh n ery e d f lot i ach d) R Co Case 15 Sh rida × 30

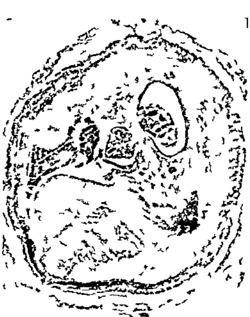


Fig 87

D st l nd of org niz g thrombu showi g v se la granul t well as blood-sp ces formed by t c tion R. Co Case 33 PTAH × 25



FIG 88

Mural thrombu shov ng ea l loss of spec f c st n ng reaction f f br i L A D B C e 31 PTAH)o



FIG 8)

The ne tain d by h n it xyh -osin Not esem blance fag in f bri t hyalinized llig n H E 90



FIG 90

Lam nated th ombus quite acellul and v scul r super ficially resembl ng hyalu ed coll gen (cf FIG 91) R Cor Case 29 H E × 45



FIG 91

The same showing streaks of f brin in the depo t PTAH × 90

properties A thrombus previously filling the whole lumen may retract from most of the vessel wall so that the circulation is partially restored (Fig 75) Often however it remains tacked to the wall at several points giving rise to the crescentic spaces at the periphery that later form the marginal blood sinuses (Fig 45)

Occasionally contraction may be enough to detach the superficial layer of an atherosclerotic plaque from its deeper layers (Fig 82) creating a cleft into which bleeding may occur similarly central cicatricial shrinkage later on may lead to wrinkling of the fibrous periphery of the plaque (Fig 83)

Should the occluding thrombus remain anchored to the vessel wall all round its periphery recanalization may be effected by the persistence of large blood channels in the clot (Fig 84) In Fig 85 a large haematoma in the plaque has initiated thrombotic occlusion of the lumen followed by recanalization of this type As the fibrin becomes organized spaces are left which confluesce towards the tail-end of the clot Such channels may be quite numerous (Fig 86) and their presence at the distal end of an organized thrombus may be due to the fact that the latter has not been subjected to the same moulding effects by the blood-stream as at the proximal end Formations of this type could hardly result from organization by granulation-tissue although both types may coexist (Fig 87) presumably depending on the vagaries of the vascular supply

FIBRIN OR COLLAGEN

In recent thrombi fibrin stains an intense purple with PTAH At an early date it loses its specificity at first staining patchily (Fig 88) and later on a light brown like collagen At this stage in haematoxylin-eosin sections it is barely distinguishable from the surrounding collagen (Fig 89) and so may escape notice in routine autopsy sections

Fig 90 shows a laminated thrombus stained by haematoxylin-eosin which superficially resembles collagen It is however paler and closer inspection reveals that it is quite acellular and avascular PTAH (Fig 91) shows streaks of fibrin in the deposit and there is an even more streaky appearance with Azan (Fig 92) This equivocal reaction with Azan is very common in superficial plaques parts staining deep blue like mature collagen while others are pale blue or red There is however no break in the continuity of the individual fibres parts of which may be blue others red *Clark et al* (1936) noting a similar appearance in some of their cases reported that well preserved fibres staining as collagen are seen side by side and even dove-tailing within fibrin-staining bands

Since fibrin retains its affinity for carmine for a longer period than with PTAH there is reason to believe that such plaques consist of fibrin in the process of being transformed to collagen This is an important point since the paucity of recognizable intermediate stages between arterial thrombosis and collagenous plaques – for example cicatrizing granulation tissue – is a formidable objection to Duguid s theories If however fibrinous laminae are converted to collagen by fibroblastic activity alone this objection is removed The full understanding of this evolution would require experimental work outside the scope of this study but one may note that recently *Levene* (1955) has examined apparently collagenous plaques by the electron microscope and found that they consist mainly of fibrin

TOTAL OCCLUSION AND COLLATERAL CIRCULATION

When occlusion of the lumen is complete and permanent then circulation can only be maintained by collateral reserves It is well known that in certain individuals complete obstruction can occur without infarction (*Wearn* 1928 *Saphir et al* 1935 *Schlesinger and Zoll* 1941) a phenomenon attributed to an unusually rich collateral circulation (*Oberhelman and Le Count* 1924) *Barnes and Ball* (1932) estimated that coronary thrombosis was a slow process which might take one to three days to cause total occlusion an interval which should allow time for the collateral circulation to become sufficiently effective to avoid massive myocardial infarction Doubtless the higher arterial pressure is a factor in ensuring that the circulating blood is coaxed into every available collateral channel

The collateral circulation is effected through the branch vessels and their ramifications including the rich adventitial plexus and it is therefore obvious why foci of severe atherosclerosis (i e old thrombosis) are so frequently found occupying a segment of the main vessel between the mouths of consecutive branch arteries Clearly part of the blood in the proximal branch is deviated through anastomotic channels to a more distal branch and so back to the main lumen

This has been well illustrated by *Hinterrutz et al* (1938) That such a phenomenon occurs and occurs frequently cannot be doubted for if it did not the rest of the vessel distal to the obstruction would be blocked by organized thrombus A fairly typical appearance at the proximal end of an occluded segment is seen in Fig 22 where several crescentic deposits are superimposed opposite the mouth of a branch artery It is not fanciful to infer that it is the current from main lumen to branch that is responsible for moulding the serial deposits in this manner

In such a case the occlusion of the main lumen is completed in a series of thrombotic episodes and so the load is not thrown all at once on the collateral circulation Eventually the residual lumen of the main vessel closes off altogether and Fig 93 shows how the diminishing current produces a series of crescentic laminae in the fibrin of a recent thrombus a pattern reproduced when it later becomes organized as can be seen in the older adjacent plaque

Before occlusion is complete the lumen of the main vessel may extend into a grossly sclerotic segment for a short distance in the form of a tapering cone emerging as an expanding cone at the distal end This is repeatedly seen in serial sections of narrowed vessels Fig 74 shows how the rotundity of the lumen is retained even in extreme narrowing and despite the eccentric distribution of the serial deposits This phenomenon is not observed in venous thrombosis and is doubtless due to the moulding effect of arterial blood Even in larger thrombi one may observe the tendency to retain a rounded fluid channel at the centre (Fig 94)

Eventually the tapering channel is sealed off altogether a process illustrated by differently stained serial sections (Figs 95 96) They show that this terminal deposit consists of concentric layers of fibrin which later undergo transformation to collagen Such an appearance could not result from the more orthodox forms of organization through the medium of a capillary network



Fig 9

The san show g st e ky react on with Az n (da k gr v = red pale g y = bl) Azan × 90



Fig 93

D n m b ng cur nt h s prod d series f resce t c f bri ous la duri g thr b sis S l r lam n t on seen n old r depo t (b e) R Co Case 3 H E × 30

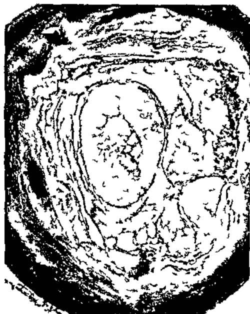


Fig 94

Recei t th bo th p ph l fibrin netwo k Blood ce tral ounded b n cl h ot co g lated L A D B Ca e 17 PAS × 25



Fig 95

Res du l l m n be g se led off by lamin of ge ng fibrin or tru collagen R. Co C se 10 Azan × 120



Fig. 96

Th sa ie 3 s tions deeper in block Total oc l ion by co i entric laminae w th nuclei (l ucocyt c) in th tersti es H E 1 o



Fig 97

Subendothelial oedema t mouth of b h te y li ed by mur l thrombus L C r un fl x C se 13 H E 65



Fig 98

Small subendothelial haemorrhage (below centr) raising intimal lining (cf F g 99) L A D B Case 17 Sheridan × 40



Fig 99

The same showing elat on of f brin netwo k in overlying thrombus to a ea of haemorrhage PAS × 40

Reference has been made earlier to the way in which an organizing thrombus causing total occlusion may become permeated by substantial vessels of arterial type formed by the extension of elastic and smooth muscle from the mouths of branch arteries or from either end of the deposit (Figs 29 40) These remarkable structures are quite out of proportion to the requirements of granulation tissue and constitute a form of recanalization The dilated state of the vasa vasorum in total occlusion suggests that they too play a small part in the collateral circulation

LOCAL FACTORS IN THE CAUSATION OF THROMBOSIS

So far I have been concerned with thrombi of substantial dimensions only and the term mural thrombi has not been applied to those small wisps of fibrin that adhere to the intima and are later incorporated in it by endothelial overgrowth These are treated in the next chapter

From time to time however one encounters small recent thrombi which afford the opportunity for looking for abnormalities in the underlying intima It is unlikely that the precipitating factors in coronary thrombosis will be discovered through morbid histology alone but observation of morphological abnormalities must constitute at least part of the answer

One great difficulty that besets the study of the intima underlying large or old thrombi is that any conclusion can be rendered invalid by the argument that the intimal changes are just as likely to be the *result* of thrombosis as the cause The following observations were all on small or recent thrombi and their causation would appear to be varied

(a) *Oedema*

Fig 97 shows early mural thrombosis at the mouth of a branch artery The underlying intimal stroma is teased out by oedema

(b) *Haemorrhage*

In Fig 98 a small superficial haemorrhage has raised the endothelial lining of the vessel and the threads of fibrin in the resultant thrombus can be traced to this point (Fig 99)

(c) *Recent thrombosis*

I have suggested earlier that overgrowth of a thrombus by an elastic membrane is essential to the health of the new intimal lining This is supported by the frequency with which a fresh thrombus is deposited on an older one which is incompletely covered by elastic (Fig 100)

(d) *Fibrinous encrustations*

A recent fibrinous encrustation incompletely assimilated by overgrowth of endothelium may form a basis for fresh massive thrombosis (Fig 101) This is really a variant of (c)

(e) *Subendothelial lipid*

Fig 102 illustrates mural thrombosis at an angle in a lumen deformed by signet-ring atherosclerosis Below the lining endothelium is a broad layer of lipid-containing macrophages not co-extensive with the clot and clearly present before thrombosis occurred

(f) *Rupture of an atherosclerotic plaque*

The causes of rupture are discussed later Loss of the lining endothelium alone may initiate thrombosis Its occurrence at the margin of an intimal tear is shown in Fig 103

(g) *Degeneration or necrosis of the intima*

If a haemorrhage or an atheromatous abscess should extend to just below the surface of the plaque the damage to the overlying endothelium may lead to thrombosis (Fig 104)

Multiple occlusions and their relation to myocardial infarction are dealt with later



FIG 100

Rece t th on bu on old d p it ot o ered by n lastic ı enbr ıe L A D B Case 20 Sherid n × 15



FIG 101

Re ent th bos on plaq e how g th l yers of f b n just b low rf ce L A D B C se 34 PTAH × 80



FIG 102

S ıall n ural thro b ı o erlyı g l yer of fo m cell R Cor C se 33 H E × 150



FIG 103

Small th o nb at site of inti n l t r L A D B Case 28 H E × 40



Fig 104

E rly thrombu on ntima r ndered degenerate by under lying atheromatou ab ess R Cor Case 13 PTAH × 40



Fig 105

Superf ial wisps of f brin being ass il ted by pl qu R Cor Case 7 PTAH × 135



Fig 106

Mural thrombus cove ing plaq e with superf cial layers separated by f brinous lam iae L A D B Case 28

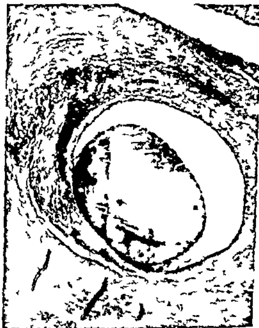


Fig 107

Ha orrh ge track ng irregul rly towards l en to initiate thron b is. L A D B Case 28 PTAH × 30

XXIII

Fibrin in Atherosclerotic Plaques

THE presence in atherosclerotic plaques of fibrin or a fibrin-like substance with special stains has attracted attention for many years *Mallory* (1914) was among the first to observe in the subendothelial layers thin flakes of this material which he took for fibrin from the blood undergoing organization a process which he regarded as responsible for the fibrous component of atherosclerosis

Leary (1934) found argyrophil fibres in this material which he therefore interpreted as *fibrinoid necrosis* of collagen due to partial infarction of the plaque and considered a frequent source of coronary thrombosis in the younger age groups *Clark et al* (1936) observed a similar substance in the fatty degenerate areas sometimes mingled with red cells and leucocytes and concluded like Mallory that it was fibrin Its presence in the floor of atherosclerotic ulcers suggested seepage into the plaque from the blood-stream

The layers below the surface endothelium (Fig 101) they regarded as surface thrombi undergoing organization They further pointed out that the argyrophil fibres observed by Leary might have been laid down by fibroblasts in the course of organization or alternatively formed by the splitting of collagen into its component fibrils before or after penetration of the plaque by haemic elements *Schlossman* (1942) tried to revive the theory of fibrinoid necrosis by showing that only a part of the material is digested by trypsin and the residue not being fibrin must therefore be necrotic collagen The argument however is unconvincing

Duguid (1948) showed that fine fibrinous encrustations on the surface of the plaque too small to be seen by the naked eye were much commoner than was supposed being present in 19 out of 50 aortas of persons between the ages of 3 and 73 who had died from varied causes These he showed *were rapidly assimilated into the plaque by overgrowth* of endothelium and organization from the surface

Fibrin unlike the other elements of atherosclerosis is rendered difficult of interpretation by the transient nature of its specific staining reactions Bleeding into a plaque rapidly undergoes thrombosis and when this is quite fresh the threads of fibrin can be seen in the form of a fine network entangling red cells and leucocytes With PTAH as stated earlier the intense purple reaction soon becomes blotchy (Fig 88) and later disappears altogether In the same way the vivid red reaction with Azan gives way to blue but the change occurs rather later It thus happens that a fairly recent laminated thrombus may come to resemble dense collagen

The appearances Duguid described in the aorta are not unusual in coronary arteries (Fig 105) and it may be noted in passing that they occur in the absence of cholesterol deposits Such small lesions could by a process of repeated accretion and organization

cause intimal thickening but it is *difficult* to see how they could give rise to the serial plaques that constitute layering each of which has the appearance of being formed complete at one time Small fibrinous encrustations may however precipitate thrombosis as was shown in the preceding chapter

Sometimes thin layers of fibrin are seen embedded in the plaque at a depth which makes it unlikely that they have been assimilated by endothelial overgrowth while retaining their staining properties and the absence of a covering elastic membrane suggests that plasma has seeped into the plaque from the surface A similar phenomenon occurs in the floor of atherosclerotic ulcers (*Clark et al* 1936) and the coarse mesh of parallel collagen fibres may lend itself to such an event (Fig 106)

Fibrinous accumulations in the deepest part of the plaque are almost certainly the sequel of local haemorrhage These too are liable to show evidence of interstitial seepage at the margins especially in the presence of degenerative softening Haemorrhages of this type may track irregularly towards the lumen causing thrombosis (Fig 107)

Similar oozings occur round the walls of unsupported vessels in degenerative foci or at the margins of fat spaces In the same way capillary haemorrhages in the vascular granulation tissue of an organizing thrombus may leave their residue of fibrin

Nowhere in this series were the appearances suggestive of fibrinoid necrosis and it is my impression that the fibrin in the plaques is derived from surface encrustations seepage *of plasma or haemorrhage into a degenerate part of the plaque*



Fig 108

Two p le staining fo ı of mucinous dege rat on Note ab nce of cells vess l and lipid L A D B Case 17 H E × 65

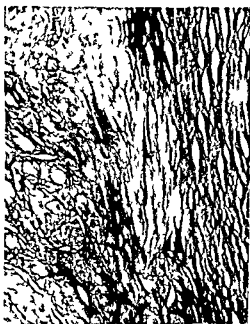


Fig 109

Deg nerate focus show g collage f b es reas d t into l h of fn f b il R Cor C se 5 Aza × 35

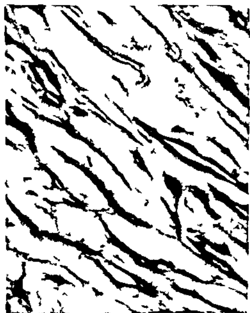


Fig 110

St e k of PAS po t n t ri l in degener te s L A D B C se 17 PAS × 380



Fig 111

Degenerate focus ı fib ous pl q harply d m c ted by layer of cal ı L A D B Case 17 H E. × 120



FIG 11

G oss swell ng of fibrous pla que due to n ucinous d gener ation No calcification L A D B Case 18 H E × 45



FIG 113

Extension of degenerat o older zo e below r ore cent tow ds centre of pictu e e h bounded by calcif d m r gin L A D B Case 18 PTAH × 45



FIG 114

Calcified area in plaque containing cholesterol cry tals. L A D B Case 28 Az n × 65



FIG 115

Large degenerate zo in plaque w th c lcif ed ma g n and fatty lake in centre L A D B Case 11 H E × 30

XXIV

Degeneration in the Plaque

DEGENERATION of the atherosclerotic plaque is a prominent feature of the larger lesions and an important factor in their subsequent evolution As the process involves mucinous degeneration calcification lipid accumulation and phagocytosis these may be conveniently bracketed together

MUCINOUS DEGENERATION

A gelatinous swelling of the intima was observed by *Virchow* (1856) to precede lipid deposition in early atherosclerotic lesions Its mucinous nature is suggested by the fact that it stains metachromatically with several dyes The literature on the subject is reviewed in Chapter XVII under Local Predisposing Factors

Streaks with a similar tinctorial reaction may also appear in the larger atherosclerotic plaques accompanied by swelling of the collagen fibres to form a pale-staining focus generally situated deeply in the plaque at the point of its greatest thickness – i e where its blood supply is liable to be poorest (Fig 108) Closer inspection reveals that the collagen fibres in this area are teased out into fine threads separated by broader ribbons of pale-staining material granular at the margins hyaline towards the centre

The fine fibrils are argyrophilic (Fig 109) and PAS positive (Fig 110) These early foci of degeneration occur in parts which are acellular avascular and free of gross lipid they have therefore been interpreted as mucinous degeneration due to inadequate nutrition – micro-infarcts in some instances As each degenerate fibre is swollen to several times its normal thickness the bulk of the focus as a whole is considerably thickened

These localized lesions are frequently surrounded by a fine shell of calcium sharply demarcating them from the surrounding collagen (Fig 111) The degenerate area may be quite small or it may involve the bulk of the plaque sparing only its surface and margins In this way a plaque may double its thickness by degenerative swelling alone quite apart from further deposits on the surface (Fig 112)

Calcification at the margins of the degenerate area may cut sharply across the fibres at right angles and there is evidence that the process of degeneration and calcification may extend periodically (Fig 113)

Considerable wedges of a fibrous plaque may undergo this type of degeneration without a conspicuous fatty accompaniment – certainly without the accumulation of lipid in macrophages In other calcified foci the fibrillar structure may be replaced at the centre by collections of cholesterol crystals (Fig 114) or fatty material in the form of large globules or irregular lakes (Fig 115) The close relationship between these patches of mucinous and lipid degeneration and the calcareous wall that surrounds them leaves little

doubt that the latter is merely a seal round a necrotic focus similar to that of a gumma or tuberculoma

The liquefaction of the degenerate contents may lead to the formation of large spaces in paraffin sections walled by a thin layer of calcium outside which the collagen fibres are abruptly interrupted at right angles (Fig 116) When such a focus (atheromatous abscess) ruptures into the lumen the walls of the residual cavity thus have the same sharply gouged appearance (Fig 117)

The avascular nature of these foci is a clue to their origin Organization of arterial thrombi is not accompanied by a rich blood-supply and as has been shown only the margins and superficial layers receive adequate nutrition derived either from the lumen or the deep plexus growing in from the vasa vasorum By the time this vascular ingrowth has occurred the central part of the plaque may have undergone infarction and subsequent extension of vessels into the degenerate area is more likely to be concerned with resorption than nutrition

This interpretation accounts for the frequent presence of small vessels extending from the enlarged vasa to within a short distance of the necrotic focus (Fig 118) It is presumably from these that capillary extension into the degenerate zone takes place (Fig 52) but by this time the damage is done How else can one explain the presence of vessels in the most degenerate parts of the plaque?

It has been shown how repeated small haemorrhages from these vessels may further increase the bulk of the pultaceous material and afford a source of cholesterol Fig 119 shows extension beyond a calcareous focus to a wider zone of necrosis not walled off by calcium and containing numerous foam-cell macrophages and a small recent haemorrhage at one corner of the concretion The foam cells are in direct contact with the interrupted collagen-fibres a not unusual appearance in atheromatous abscesses

CALCIFICATION

Demonstrable strata of calcification were observed in the plaques of roughly half of the cases investigated and were sometimes a very prominent feature Though rather more constant in the older age groups calcification was also a very common finding in those below 50 (see Table D)

TABLE D

Age of Subject	*No of Cases*	*No of blocks examined*	*Lipid Degeneration*	*of Total*	*Calcification*	*of Total*
Under 50	5	32	20	6 5	15	46 9
Over 70	7	33	16	48 5	20	60 6

In severe signet-ring deformities several calcified foci may be superimposed one in the depths of each deposit (Fig 115) Eventually these may fuse into one (Fig 1-4) It was stated earlier that deep foci of calcification appeared to cause pressure atrophy of the related media but it is likely that in the first instance the pressure was due to swelling of



FIG 116

L quefact on of d gener t zone w d thin cal ih d wall cutting across collag n f b es t right angles. L A D B Case 18 H E × 45



FIG 117

Sh rply g uged walls of ather natous abscess whi h has discharged t contents into lu n R Cor Case 13 Foot × 35



FIG 118

Vessel p ssing from m rgin of plaque towards n crotic ne but not entering it L.A D B Case 12 H E. × 60.



FIG 119

Collagen fibres interrupted at right a gles by foam-cell accumulation. Not small h morrhage at one angle of confetion L.A.D B Case 8 PTAH × 35



FIG 1 0

Degenerative swelling and calc f ation at base of plaque caus ng pressu e trophy of adjacent media L Cor Case 6 PTAH × 60



FIG 121

Calcification of fib ous pl que invol n it surfa e R Co Case 35 H E × 40



FIG 12

Organized mur l thrombus overlying calcif cat on which formerly in olved surface of plaque but not co-extensive with it L Cor Case 6 H E × 40



FIG 123

Haemorrhage into clef between c lcified layer and o lying fibrous tissue of plaque L A D B Case 32 H E × 60

the degenerate collagen fibres (Fig 1-0) Subsequent calcification by rendering the swelling permanent and immobile doubtless accentuates the atrophy especially in severe signet-ring deformities

Calcium is not always deposited at the periphery of an infarct in the plaque as described above it may be found at the centre of a small degenerate focus or scattered widely through the substance of a larger one in the form of small granules or around fat globules But its association with degeneration and necrosis is constant

During the eighteenth and nineteenth centuries calcification was regarded as the very essence of coronary sclerosis By 1935 opinion was sufficiently reversed for a careful observer like *Leary* to write from any standpoint calcification is of no importance in the aetiology of the lesions and is only significant in that a coronary vessel converted into a rigid tube is no longer subject to the influence of spasm of the media though on the other hand it is no longer capable of dilating (*Leary* 1935c)

Paterson (1936) did not consider calcification a factor in initiating thrombosis but *Horn and Finkelstein* (1940) recorded bone-formation in a plaque eroding a capillary and causing haemorrhage From the present study it is safe to say that a calcified plaque is much less prone to haemorrhage thrombosis or rupture than a plaque which has undergone fatty softening

Thus calcification may involve the surface of a plaque without necessarily causing thrombosis (Fig 1-1) Incidentally this shows that nutrition from the lumen is not invariably maintained to a depth of 0 35 mm as *Geiringer* (1951) suggests Calcified plaques may lie immediately below a thrombus or organized deposit (Fig 1-2) but unless the two are co-extensive there is no reason to postulate a causal connection

In short calcification does not appear to be an essential or even an important feature in the progress of the atherosclerotic lesion Calcified plaques are said to contain less cholesterol than the normal intima (*Hirsch and Weinhouse* 1943) but so far no one has demonstrated that calcium actually protects the intima from lipid degeneration *Harrison* (1933) showed that experimental atherosclerosis does not occur over calcified patches in the *media* but the latter lesions were more like those of Monckeberg s sclerosis than human atherosclerosis

In the present series the only complications that might be considered attributable to calcification apart from medial atrophy were occasional narrow clefts at the margin of an affected focus At first these were deemed artefacts due to cutting across a calcareous artery with a heavy knife prior to processing and indeed this may account for some of them but in others the clefts were associated with local vital reactions and alternative explanations must be sought These reactions include haemorrhage (Fig 1-3) fibrin or albuminous fluid between the calcified focus and the rest of the plaque and even endothelial or giant cells lining the cleft

In themselves these isolated phenomena may be unimportant but they do suggest that a calcified sliver is liable to partial dislocation from the more pliable fibrous tissue of the plaque and that this may on occasion give rise to intimal haemorrhage and its sequelae A similar observation was made by *English and Willius* (1943) There are two ways in

which such dislocation might occur by spasmodic contraction of the media or by retraction of the surrounding fibrous tissue

The second is more likely I have postulated a degenerative focus in which the collagen fibres first swell and then become surrounded by a shell of calcium This would prevent the affected wedge from contracting evenly with the rest of the plaque In time the plaque comes to give the impression of being tightly contracted round a disproportionately large calcified block sometimes to the extent of compressing the media or distorting the vessel s outline (Fig 124)

LIPID DEGENERATION

Lipid deposits in the plaque are a highly characteristic feature of the disease indeed according to most authorities they constitute the essential lesion of atherosclerosis The lipid may be (*a*) intracellular in the form of macrophages with a foamy cytoplasm (*b*) extracellular in the form of rounded globules or crystalline deposits

The foam cells are almost certainly macrophages brought in from the margins of the plaque by small blood vessels Even in small atherosclerotic plaques a collection of lymphocytes at either margin is a familiar feature and in the presence of abundant lipid larger mononuclear forms are observed (Fig 125) These cells are no longer believed to be inflammatory in origin as was suggested by *Boyd* (1928) and their function is regarded even by adherents of the cholesterol-imbibition theory as phagocytic

Anitchkov (1933 p 288) in a study of experimental atherosclerosis was able to observe all transitional forms between the small lymphocyte and monocytic cells on the one hand and the large lipid cells on the other so that development of the lipid cells from the free mononuclear cells probably derived from the blood would seem to be the most plausible hypothesis of their origin

(*a*) DEEP LIPID ACCUMULATION

The route by which the macrophages are conveyed to a deeply situated focus of degeneration where the lipid is separated from the lumen by a thick layer of dense and avascular collagen (Fig 126) seems fairly clear It is quite unlikely that the macrophages could penetrate the plaque from the lumen and one must conclude that they are carried to the degenerate zone by the ingrowing capillaries In such a case the accumulation of cells is not the primary lesion as is widely maintained but a secondary phagocytic phenomenon The acellular nature of the early degenerative foci (Fig 111) supports this view

The source of the lipid has always been a major problem According to *Duguid* (1946) it is the product of fatty degeneration in a thrombus and on this hypothesis it would be consistent with what has already been described to regard it as a late stage in the degeneration of an organized clot The same author believes that fatty change can occur in fibrin thrombi but he gives no grounds for this belief *Winternitz et al* (1937) by injecting the intimal vasculature of aortic plaques and clearing by the Spalteholz technique were able to demonstrate vessels all round the softened foci and concluded that capillary haemorrhage was the source of the lipid The following extract from their paper is explicit

There appears to be a gradual accumulation at the site of the haemorrhage of fatty



FIG 124
D gene te z ne w th calci n h ll di p po t o iat ly bulky omp red t f b o at P phe y of pl que L A D B Case 11 H E × 30



FI 125
Mon nu l a ll t n gin of th i t b s howi vari tion iz d a l f h ng vtoplasm L A D B C se 30 H E 840



FIG 1 6
Typ l ppea ic of d p f tty depo t sep rated f o n un en by l v r f d n collagen R Co Case 12 H E. 35



FI 12
Conglu na d ed cell t pped n f b n a n lat d lat r to pl



FIG 128

Fat droplets extracellular and intracellular in laminated wh te thrombus in aneurysm l sac Ao ta (Ca e not in series) Sud n III × 960



FIG 12)

Same case Pe iv scular accum l t on of l pid n fibrou w ll of neurys n l sac *Sudan III* × 30



FIG 130

The san e using polaroid *screens to d monstrate aniso-tropic* natur of lip d



FIG 131

Organizing hae orrhage i nodular goitre show ng cholest ol cl fts g nt cells, i acrophages (ont in h h emosider n) and proteinou mush H E × 125

material which is stainable with Sudan III and which frequently contains the so-called cholesterin clefts giving the appearance of the classical atheroma It is reasonable to suppose therefore that this fatty material is derived from and eventually replaces the blood of the original haemorrhage a process analagous to the apparent changes observed in haemorrhages in thryoid adenomas and in cavernous haemangiomas Such a conclusion is borne out by the fact repeatedly confirmed that a typical yellow atheromatous plaque may on careful examination by the methods outlined above show at its periphery a network of capillaries containing red blood cells and anastomosing outside the zone of fat and necrosis with obviously well-delineated and well-functioning blood-channels

This argument does not take into account the fact that focal necrosis occurs in the first place in parts of the plaque that are avascular and free of recognizable lipid Once these areas become vascularized however foam cells appear *and thereafter the hypothesis is* valid Indeed before reading the above passage I had concluded that capillary haemorrhages into a necrotic focus repeated over a long period constitute at least one source of cholesterol and set in motion the vicious cycle that ultimately results in an atheromatous abscess The extra-cellular lipid accumulations at the centre are of course no more than the debris of broken-down foam cells

There is however another source of cholesterol It has not been proved that collagen or fibrin are subject to lipid degeneration but it is certain that as a mural thrombus retracts a variable number of red cells are trapped in the fibrinous network and squeezed between its laminae and must ultimately in broken-down form constitute an element in the deposit capable of providing a source of cholesterol (Fig 127)

In testing this idea frozen sections of a laminated thrombus in an arteriosclerotic aneurysm were stained by Sudan III and examined under polaroid screens If Duguid s theory is correct i e that the lipid is due to fatty degeneration in a thrombus something of the same sort should occur in the serially deposited thrombi in an aneurysmal sac

Fig 128 shows scattered throughout the granular haemic debris minute droplets of extracellular fat similar in appearance to the subendothelial fat dust of early atherosclerosis also clusters of larger granules apparently garnered by macrophages Both are isotropic Deeper down where the periphery of the thrombus has undergone some degree of organization is a broad *lipid layer mostly extracellular and partly anisotropic Leading* from this into the fibrous wall of the sac are perivascular chains of foam cells swollen with anisotropic lipid in its greatest concentration (Figs 129 130)

The inference is that a thrombus undergoes fatty degeneration isotropic globules being taken up by any macrophages surviving within the clot or capable of entering it In the oldest part the lipid is anisotropic either as a result of chemical synthesis or accumulation of the more insoluble components over a long period In short it is clear that many of the features of lipid accumulation in atherosclerosis are also present in degenerate arterial thrombi

Now the relation of cholesterol to atherosclerosis has been energetically debated particularly (as was shown in Part I) in connection with fatty streaking experimental atherosclerosis and recent work on serum lipids Without prejudice to the biochemical

findings the histopathologist may note that (1) Cholesterol is present in every animal cell is very stable and is relatively insoluble (*Schonheimer* 1931) It is certainly present in red blood cells (2) Cholesteatomata surrounded by altered blood pigment are not unusual sequelae of haemorrhage into a nodular goitre (Figs 131 132) They have also been observed to follow traumatic haemorrhage in bone (Fig 133) (3) Cholesterol like calcium tends to accumulate in necrotic material e g caseous tubercles (*Caldwell* 1919) and their cholesterol content may be increased by feeding cholesterol to tuberculous animals (*Jaffe and Levinson* 1925) a fact that may help to explain the excess in the plaques of diabetics and other hypercholesterolaemic subjects

It is thus possible to account for the presence of cholesterol in an atheromatous abscess without necessarily invoking a disorder of lipid metabolism *Leary* (1938) objected that normal blood contains less than 1 per cent of total fats whereas most of the fat in atherosclerosis is cholesterol but this ignores the cumulative effect of recurrent small haemorrhages over a long period and the resistance of cholesterol to absorption

Moreover as *Duff* (1935) pointed out no one has postulated a disorder of calcium metabolism to explain calcification in atherosclerosis

(*b*) SUPERFICIAL LIPID ACCUMULATION

Less easily explained however are the broad layers of foam cells observed on the surface of an atherosclerotic plaque immediately below the lining endothelium (Fig 134) Admittedly such appearances were observed in a few cases only and a study of serial sections generally revealed that these layers were only an outcrop from a more deeply placed atheromatous focus communicating with the surface of the plaque along an oblique cleft a phenomenon related to *dissection* which is discussed at the end of this chapter

This is not always so however and it must be conceded that superficial foam cell accumulation independent of deep-seated softening is a phenomenon not readily explained by the thrombogenic hypothesis of atherosclerosis *Duguid* (1948) is prepared to admit that superficial lipid may be due to disordered metabolism and therefore of a different nature from the deeper deposits and by feeding rabbits with cholesterol he has satisfied himself that experimental lesions are produced by repeated endothelial overgrowth of foam cells which have migrated from the circulating blood to the lining of the vessel (*Duguid* 1954) He has therefore postulated a dual pathology in atherogenesis but this work requires fuller confirmation

This is an opportune moment to introduce very briefly the theories of *Leary* (1934 1935a 1936a 1941) Basing his views on experimental atherosclerosis induced in rabbits by feeding cholesterol he concludes that the capacity of humans to metabolize cholesterol diminishes with age The excess lipid is conveyed from the blood-stream to the intima by globular lipophages and is later taken up by phagocytic cells with the properties of fibroblasts In younger subjects the cholesterol acts as an irritant and provokes a fibrous response and as their ability to metabolize cholesterol is greater a fibrous plaque results in old age the fibrous response is less and the lipid tends to accumulate hence the frequency of atheromatous abscesses in the aged



Fig 132

O gan d ha t iorrh ge n t odule g tr — choles-teaton a u und d by f b o t H E 35



Fi 133

O g n zing h n t na n bo e foll w g tr u n w th fatty p g nt ll and m croph contai ng h no ider H E 45



Fig 134

Supe fici l l p d deposit s s ed tely bel w lin ng endo-th l u L A D B Case 30 PTAH × 160



Fig 135

Peri ascul r h mos d rin extend ng f om f bro b se of thero tou abscess to d entually phat ck R Co Case 13 PAS × 110

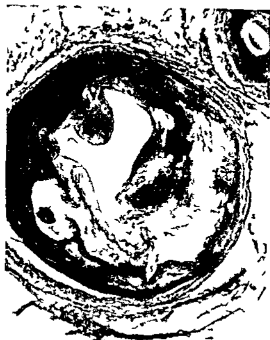


FIG 136
G eat d stortion of lumen au ed by former tears and ruptures L A D B Case 28 Azan × 20



FIG 137
Healing by g nulatio afte rupt re of pl que l n n ted f gments of which re st ll s en R Cor Case 10 A n × 30



FIG 138
Overlappin deposits sh ply separ ted by elast c layer predisposing to d ssect on L A D B Case 5 Sherid n × 125

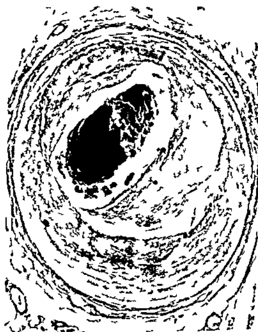


FIG 139
Oblique l yer of degenerat e softeni g between 2 deposit pred sposi g to d ssection L A D B Case 5 Fo t × 15

However *Horn and Finkelstein* (1940) in a study of 100 fatal cases of coronary disease were unable to correlate old age with atheromatous abscesses and the present study supports their views (see Table D) It may therefore be seen that Leary s theories readily explain the superficial lipid but not the deeper foci He also made much of cholesterol-laden cells which he observed half way through the lining endothelium and which he regarded as lipophages passing through the plaque from the blood-stream He does not appear to have considered the possibility that these might simply be macrophages which had derived their cholesterol content from the red cell residue in the plaque and which had been observed in the act of passing back *into* the lumen in the course of phagocytosis

PHAGOCYTOSIS

This has already been dealt with in relation to lipid but it is also concerned in the removal of altered blood-pigments Now some have objected that if cholesterol is derived from broken-down red cells there should be more evidence of haemosiderin in atherosclerotic plaques But in fact Prussian Blue preparations reveal a good deal more haemosiderin than superficial examination of haematoxylin eosin sections leads one to suspect much of it dispersed in fine extra-cellular particles Indeed it is only when haemosiderin is concentrated within macrophages that it becomes conspicuous – e g Fig 135 where siderophages may be traced from a haemorrhagic focus in the plaque to the adventitial lymphatics

In any case if the earlier observations on arterial thrombi are correct one would not expect to find the same concentration of haemosiderin as in a venous thrombus Firstly an arterial thrombus is mainly fibrinous next the red cells trapped within it may have their haemoglobin washed out of them within a few days lastly the scanty vascular supply imposes a restriction on the number of available phagocytes and such blood-pigment as may be left in the plaque must remain unconcentrated and dispersed

Incidentally *Paterson* (1954) has employed the Prussian Blue technique on gross specimens and detected large amounts of unsuspected haemosiderin in human aortas which had not shown any macroscopic evidence of haemorrhage

RELATION OF AGE TO DEGENERATIVE CHANGES

In this series the various types of degeneration did not appear to be closely related to the subject s age To test this the vessels of the 5 cases under 50 were compared with the 7 over 70 involving the examination of 65 blocks of the main divisions of the coronary arteries (see Table D) No conclusion can be drawn from this small series but it can at least be stated that it does not support the idea that lipid degeneration is significantly commoner in the older age groups Calcification while more frequent in the over-70 group is also present in nearly half the under-50 group

RUPTURE AND DISSECTION OF THE PLAQUE

Rupture of an atherosclerotic plaque is a fairly common finding The predisposing

cause of course is degenerative softening in the depths of the plaque with gradual extension towards the surface When the roof of an atheromatous abscess gives way (Fig 104) the contents are discharged into the lumen leaving a cavity with sharply gouged walls (Fig 117)

Rupture may be precipitated by haemorrhage into the abscess and complicated further by secondary thrombosis (Fig 68) *Leary* (1934) regarded this as the usual mode of death in older age groups He believed that the blood from the lumen might also rupture *into* the abscess and so initiate thrombosis It is very probable that the force of the arterial blood is capable of disrupting the plaque still further and Fig 68 shows a tear extending right down to the media causing great deformity of the lumen This is further emphasized in Fig 136 where multiple foci of softening have resulted in a lumen with a bizarre outline and irregular healing has formed ridges and clefts on its lining Should thrombosis follow the resultant granulation tissue may fail to obscure completely the lineaments of the original rupture (Fig 137)

There is another very distinctive type of accident which I have termed dissection in which the line of cleavage is along the former junction of two overlapping deposits There is a natural plane of fission at this level the serial deposits being separated by an elastic membrane (Fig 138) and not firmly knit together by a process of vascular organization as was stated in the section entitled Layering in Chapter XX This weakness is exaggerated by the tendency to degenerative softening in the deeper part of the superficial deposit which is furthest removed from the main bloodstream and incapable of deriving adequate nutrition from the deeper layer (Fig 139)

This is accentuated as in the deeper abscesses by microhaemorrhages from the vessels growing in from the margins and the softening tends to extend along an oblique plane from the depths of the plaque towards the surface It has already been shown that superficial lipid accumulations *are generally no more than an outcrop from one of these strata* In the same way larger haemorrhages are liable to cause rupture into the lumen raising the margin of the overlying deposit in a very characteristic manner (Fig 140) As with the more conventional atheromatous abscess such an accident may lead to thrombosis

What happens to the particulate debris discharged into the lumen following rupture of an atheromatous abscess is a matter of speculation but it is reasonable to suppose that some of it may cause at least a temporary occlusion of the finer twigs in the distal reaches *of the* vessel Cholesterol embolism is not unknown (*Flory* 1945 *Meyer* 1947) and *Zak and Elias* (1949) have shown that it can result from coronary atherosclerosis producing small foci of necrosis or fibrosis in the related myocardium

XXV

The Relation of Coronary Occlusion to Myocardial Infarction

In a rough attempt to gauge the total degree of coronary insufficiency and the relative frequency of the lesions in the main branches the following grades of obstruction were recognized (1) Total occlusion (2) Subtotal occlusion (3) Severe narrowing

Total occlusion was due to (*a*) *Thrombosis* recent (Fig 94) organizing (Fig 70) or fibrous (Fig 141) The last-mentioned although regarded by *Koch and Kong* (1932-33) as a separate entity is treated here as the end-stage of organized thrombosis (*b*) *Haemorrhage* into the plaque either raising the intimal lining and compressing the lumen or damaging it and initiating thrombosis Examples of how this occurs are given in Figs 66 and 67

Subtotal occlusion is a term reserved for those instances where a minute vascular channel quite inadequate as a functioning conduit was preserved in any of the following Extreme signet-ring deformity (Fig 142) extreme concentric narrowing (Fig 74) excess atheromatous softening with or without haemorrhage (Fig 143) marginal retraction of a thrombus (Figs 45 144) recanalization of a thrombus (Fig 41)

Severe narrowing is a somewhat arbitrary term applied when the lumen was reduced to a circle 2 mm in diameter or a slit not more than 1 mm in its shorter diameter

The degree of narrowing at some point in each of the main branches was then related to the presence of an infarct and the mode of death The analysis is set out in full in Table F but the relative frequency of disease of the three branches is summarized in Table E

TABLE E

Degree of Narrowing	*L A D B*		*L Circumflex*		*R Coronary*	
Total Occlusion	Old 7 Recent 6	13	Old 4 Recent 1	5	Old 6 Recent 2	8
Subtotal Occlusion	Old 4 Recent 1	5	Old 1 Recent 1	2	Old 6 Recent 0	6
Severe Narrowing	15		10			
No Significant Narrowing	6				14	

It will be seen that out of a total of 39 cases 33 had severe to complete occlusion of the left anterior descending branch 25 of the right coronary and 17 of the left circumflex branch From a functional standpoint blockage was complete in the left anterior descending branch in 18 in the right coronary in 14 and in the left circumflex branch in 7

These figures support those observers who have found the left coronary artery and its branches more frequently involved than the right (*Hearn* 1923 *Faulkner et al* 1924 *Wolff and White* 1926 *Hamman* 1926 *Parkinson and Bedford* 1928 *Levine and Brown*

1929 *Wolkoff* 1929 *De Coursey* 1934 *Saphir et al* 1935) They disagree with those who find the right coronary artery as frequently or more frequently affected (*Barnes and Ball* 1932 *Master et al* 1937a *Horn and Finkelstein* 1940)

TABLE F

Case No	*L A D B*	*L Circumflex*	*R Coronary*	*No of vessels affected*	*Infarction*	*Type of death*
1	T (R)	—	—	1	Ant (R)	Gradual
	S T (O)	S N	S N	3	—	Sudden
3	S N	—	S N	2	—	Gradual*
4	S T (R)	—	—	1	—	Sudden
5	T (R)	—	S N	2	Ant (R)	Gradual
6	S N	—	—	1	—	Sudden
7	S N	—	T (O)		Ant (O)	Sudden
8	S N	—	—	1	Post(O)	Gradual
9	T (O)	S N	S N	3	Post(O)	Sudden
10	S N	S N	T (O)	3	—	Sudden
11	S N	—	S N	2	Ant (R)	Sudden
12	S N	S N	—		Ant (R)	Sudden
13	S N	T (O)	T (O)	3	Ant (O)	Gradual
14	S N	—	—	1	—	Sudden
15	S N	S N	S T (O)	3	Post(O)	Sudden
16	T (O)	S N	S T (O)	3	Ant (O)	Gradual
17	T (R)	—	—	1	Ant (R)	Sudden
18	S N	—	S N		—	Gradual*
19	S N	S N	S N	3	Post(O)	Sudden
o	T (O)	—	T (O)	2	P (O) A (R)	Gradual
1	T (O)	T (O)	—	2	Ant (O)	Sudden
	—	—	S T (O)	1	—	Sudden
3	—	—	S N	1	—	Gradual*
24	S N	—	—	1	—	Sudden
	S N	S T (R)	T (O)	3	—	Sudden
6	T (O)	T (O)	—	2	Ant (O)	Sudden
27	—	—	S T (O)	1	—	Sudden
8	T (R)	T (R)	—	2	Ant (O)	Gradual
9	—	—	S N	1	—	Sudden
30	T (R)	—	—	1	—	Sudden
31	T (O)	—	S T (O)		Post(R)	Sudden
32	T (O	S N	—	2	—	Sudden
33	S T (O)	S T (O)	T (O)	3	Ant (O)	Gradual
34	T (R)	S N	T (R)	3	—	Sudden
35	—	—	S N	1	Post(R)	Gradual
36	—	S N	T (R)		Post(R)	Gradual
37	S T (O)	—	S T (O)		—	Sudden
38	S T (O)	T (O)	S N	3	Ant (O)	Sudden
39	S N	—	—	1	Ant (R)	Gradual
40	MATERIAL INCOMPLETE					

T = Total occlusion
S T = Subtotal occlusion
S N = Severe narrowing
R = Recent
O = Old
* Died from other causes

All three main vessels were severely diseased in 11 cases two vessels in 14 and only one in the remaining 14 *Of the 2– cases exhibiting signs of old or recent infarction* two or even all three vessels were seriously diseased in 17 (Figs 145-8) This gives some support to the view of *Saphir et al* (1935) that occlusion of more than one branch is required to produce infarction This is only approximately true however since in 5 cases of infarction only one vessel was seriously narrowed whereas 3 other cases (Nos 2 10 and 34) had



FIG 140

D ssect on of plaque following haem o hage i to focu of softe   g between depo ts R Cor C e 34 Sherid n × 35



FIG 141

Total o cl i n of f brous type L A D B Ca e 9 H E × 30



FIG 142

S br t l o l   on by e t n e s gn t ring def   ty R Cor C   31 PTAH × 30



F G 143

S br t l o l   on d e to haemorrhage nto atherom tou bscess. L A D B   Case 30 H E × 20.



Fic 144

Subtotal oc lusion due to narg nal retr ction of recei t th ombus L A D B Case 20 Aza 15

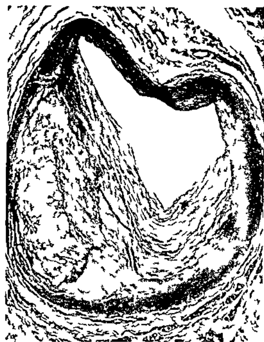


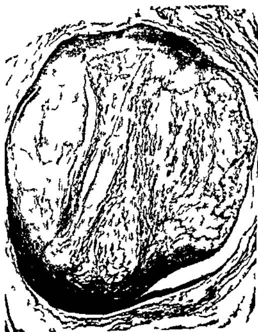
Fig 145

L A D B showing se re n ow g C 13 H E 5



Fig 146

L Ci cumflex branch of me c se showing subtotal occlusion by recent h morrhage i to athe o natou abscess H E × 45



Fic 147

Anothe pa t of L C rcu nfl x br nch of same c se showing tot l occl ion by org nized th on bo i H E × 30

severe to total occlusion of all 3 major branches without visible infarction This clearly illustrates the variability in the collateral circulation of different hearts a subject more fully discussed in Chapter VIII As was to be anticipated all the cases of gradual death showed myocardial infarcts excepting those who died of unrelated causes On the other hand 14 of the 25 cases of sudden death showed no visible infarct This is in accordance with the view that many cases of sudden death are due to acute myocardial ischaemia before infarction has had time to cause visible lesions while those who survive the acute attack and die days or weeks later exhibit the familiar features of a cardiac infarct

XXVI

The Coronary Arteries and the Rest of the Cardiovascular System

REPRESENTATIVE samples of visceral and skeletal arteries were removed at each autopsy for comparison with the coronary lesions These included cross-sections of the thoracic and abdominal aorta the renal artery the brachial artery at the level of the elbow-joint and the popliteal artery at the level of the knee-joint

Broadly speaking it can be said that intimal lesions comparable to those in the coronary arteries were present in the aorta and popliteal arteries but that in the brachial and renal arteries the intimal lesions were inconspicuous and medial degeneration predominated The microscopic lesions are described first the correlations are treated later

THE AORTA

Every case investigated showed atheroma always more severe in the abdominal portion especially in the 2-3 inches between the origin of the renal arteries and the bifurcation In a rough attempt to gauge the severity three grades were recognized based on the extent of surface involvement degree of ulceration and the microscopic characters (thickness of plaques degree of degeneration thinning of the media destruction of elastic and so on)

+ indicates anything from fatty streaking to a few widely separated plaques with an intact surface

++ indicates numerous plaques some with ulceration

+++ indicates large confluent areas of ulceration

Microscopically the features of coronary atherosclerosis are generally reproduced modified of course by the width of the aortic lumen and the absence of occlusion or its complications As with the coronary vessels the appearances indicate that advanced lesions owe more to thrombosis than to lipid infiltration or intimal fibrosis

Thus *layering* is a regular feature with the deposits either uniformly superimposed (Fig 149) or overlapping (Fig 150) although in neither case is the width of the lumen significantly reduced The button-like thickenings round the mouths of branch vessels so characteristic of aortic atherosclerosis show the same type of layering as their coronary counterparts (Fig 151)

Newly formed *elastic tissue* either as a finely fibrillar tangle at the base of the plaque or in the form of serial marginal membranes (Fig 152) is again common as is the extension of *smooth muscle* from the vessel wall (Fig 153)

Intimal vascularization follows the broad patterns outlined in coronary plaques i e with superficial and deep plexuses and hypertrophied vasa vasorum passing transmedially to

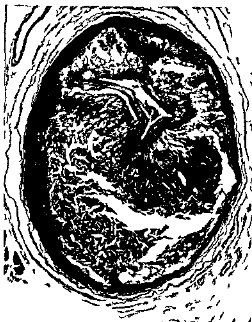


Fig 148
R Co o y of s me sh w ng subtotal occlu on by olvi g h emo hage in l ge the o rou b ess H E × 35

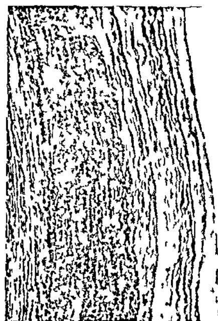


Fig 149
Layering with d posits unif n ly uperimposed Ao t C se 18 Sherid n × 60



Fig 150
Lay ri g w th dep t overl pp g A rt Case 5 Sh ridan × 35



Fig 151
Lay ring ro d mo th of b ch rt ry (f F g 4) Aort Case 10 Sherid n × 15



FIG 15

Recurrent elastic membranes continuous with elastic lamina at n gin of plaque Aorta Case 11 Sheridan × 40



FIG 153

Same essel showing ingrowth of n uscle app rently derived f om nusculo-el stic l yer PTAH × 40

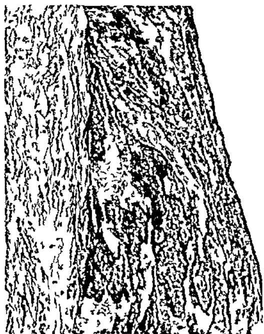


FIG 154

Mural th ombus with high f brin content in forn of coarse network enclosing red cells (cf F g 76) Aorta Case 5 PTAH × 150



FIG 155

Wi p of f brin on su f ce of atheroscl rotic plaque Aorta Case 5 PTAH × 40

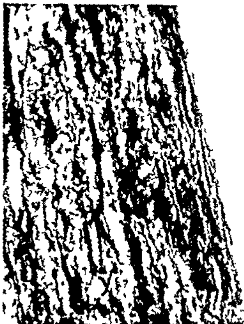


FIG 156

Cranular swel i g of fibres n plaque Aorta Case 14. Azan × 430

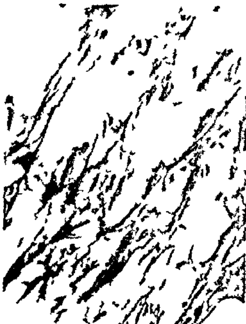


FIG 157

Myx n to s degenerati n th p der shaped i l Aorta C se 9 PTAH 430



FIG 158

PAS pos ti e streaks n degenerat plaque Aorta C se 33 PAS 40

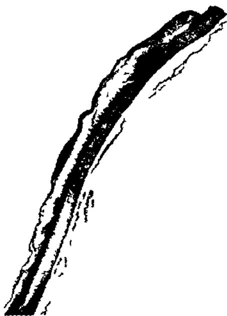


FIG 159

D secti n of the plaque with uperficia lipid outer p Aorta Case Azan 8



Fig 160

C o s edial atrophy t base of ath ro atous abscess Aort C se 25 She ida x 30

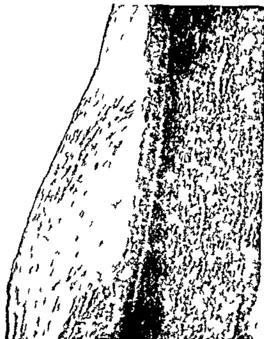


Fig 161

Superfic l depos t of age ng la n ted fibrin Ao ta Case 6 PTAH × 30



Fig 16

Same case Superf c al foam-cell deposit Aorta Aza × 85



Fig 163

F t dust below n timal endoth l u m f tty t e king Aorta (Case not in ser es) Froze sect on Sud n III × 300

link up with the deep plexus But the vascularity is directed to the requirements of the plaque and not at all to the formation of a collateral circulation as in the case of severe coronary narrowing This may account for the impression gained (from an admittedly inadequate survey of aortic plaques) that superficial plexuses are more prominent in the aorta and transmedial ingrowths of vasa less than in their coronary equivalents The deep plexus again appears to follow marginal retraction but in this case there is little need for collateral channels

Haemorrhages into degenerative plaques augment the atheromatous lesions as in the coronary vessels *thrombosis* is of the mural type with the same high proportion of fibrin (Fig 154) and the same tendency to be compressed into laminae parallel with the vessel wall and wisps of fibrin as shown by *Duguid* (1948) are found adhering to the surface (Fig 155) or undergoing assimilation into the body of the plaque

Degenerative changes follow the familiar pattern The collagen fibres undergo a finely granular swelling (Fig 156) or disintegrate to form a myxomatous matrix containing spider-shaped nuclei (Fig 157) The abundance of PAS-positive material indicates a mucinous change (Fig 158) Lipid accumulates in the depths of the plaque into which microhaemorrhages occur Larger haemorrhages may be followed by rupture of the plaque and secondary thrombosis Oblique degenerative fissures in the plaque may lead to dissection or cause lipid outcrops to appear below the surface (Fig 159) Calcification of course is all too common and even foci of ossification Focal atrophy of the media is particularly common below large plaques and the degree and extent of musculo-elastic destruction are sufficient to account for the so-called arteriosclerotic aneurysms (Fig 160)

Superficial foam-cell accumulations again raise the question of the dual nature of atherogenesis Figs 161 and 162 show neighbouring and purely superficial excrescences on the intima of the same aorta the one largely fibrinous the other almost wholly fatty In an unsuccessful attempt to answer this problem frozen sections of superficial aortic lesions were examined

In the main the morphological observations of others on fatty infiltration were confirmed Below the endothelium at the margins of a fatty streak and therefore presumably representing the earliest form of the accumulation a fine isotropic fat dust can be seen (Fig 163) Below this and lying between the elastic laminae are macrophages containing isotropic lipid droplets (Fig 164) These appear to be spindle-shaped but sections parallel to the surface show they are discoid the shape possibly being determined by intra-arterial pressure In older plaques the lipid becomes anisotropic and connective tissue is formed as is shown by paraffin and frozen sections of the same lesion using polaroid screens (Figs 165-7)

Leary's theories of atherogenesis have been referred to under Superficial Lipid Accumulation (Chapter XXIV) and were elaborated in Part I under Experimental Atherosclerosis (Chapter IV) He believes that the cholesterol is taken up by fibrolipophages – cells which have both phagocytic and fibroblastic properties – and that these lay down the fibrous tissue in the plaque Fig *168 shows a cell in an aortic plaque which answers* his description of a fibrolipophage He has however no very satisfactory explanation

for the manner in which the cholesterol reaches the deeper parts of the plaque where it appears to evoke a similar reticulin response (Fig 169)

THE POPLITEAL ARTERIES

Popliteal atherosclerosis is common affecting 25 of the 27 arteries examined (see Table G) A significant narrowing of the lumen may occur and this may be extreme (Fig 170)

TABLE G

Case No	Age	A rta	Brachial	Popliteal	Renal	Cor y*	B P
1	50	+		+		1	
2	51	+				3	
3	67	+		?	MF		Normal
4	66	+				1	
5	54	++	?			2	240/150
6	55	++			?	1	
7	74	++					
8	49	++	+	++	MF	1	240/130
9	48	++	+	+	+	3	200/100
10	68	++			?	3	
11	68	++		?			160/80
12	75	+	MF	?	O	2	
13	59	++	O	?		3	160/130
14	55	+	MF			1	145/80
15	78	+++		+		3	
16	61	++	+	+	MF	3	270/115
17	54	+	MF	++		1	
18	70	++	O	+	O	2	145/70
19	0	+	MF	++	MF	3	
0	37	+	MF	O	+		No l
21	64	+	O	++	MF	2	
22	58	+	O	O	O	1	
23	74	++	MF	++	O	1	170/70
24	75	+	MF	+	+	1	
25	59	+++	+	+++	?	3	210/110
26	67	+++	MF	+	+	–	
27	59	++	O	+	MF	1	
28	66	++	MF		+	2	240/140
29	69	+++	O	+	MF	1	
30	71	++	+	+	+	1	Nor l
31	51	+++	O	+	+		
32	47	+	+	++	O	2	
33	59	++	?	+	O	3	145/75
34	53	++	O	+	MF	3	No mal
35	80	++	+	+	MF	1	100/40
36	48	++		++	+		60/150
37	64	+	O	+	MF	2	
38	63	+	O	+	+	3	
39	67	+++	+	++	+	1	
40	MATERIAL INCOMPLETF						

* = No of Coronary branches occluded by atherosclerosis (see Table E)
MF = Medial fibrosis no atheroma
O = No atheroma or medial fibrosis
? = Unknown

In general it can be said that the lesions correspond more closely to coronary atherosclerosis than in any of the other arteries in this series



Fig 164

M croph g be ri g 1 ot op lip d granul below end th l u 1 and between elast c l min e Ao ta (Case not in ser es) F ozen section Sud n III × 400

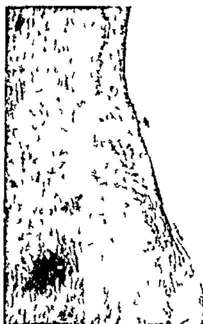


Fig 165

Paraff n sectio of ll therosclerotic plaq how g f t sp ces and f brous ti s Ao t (Case not n series) H E × 40



Fig 166

The same plaque show g lip d in m croph ges. Fro en sect on Sud n III × 40



Fig 167

The same sect on showing lip d to be an sotrop through pol ro d screens.



FIG 168

F brol pophage ( ) howing lipid granules n cytopl m nd tapering branches at e the pole Aorta Case 3 PTAH 1020



FIG 169

Atheromatous bscess with n asse of cryst ll ne cholesterol in reticulin netwo k Aorta Case 35 Foot × 100



FIG 170

Extreme signet-ring deform ty showing layer g vascular clefts between depos ts and degeneration of deeper layers Popl teal artery Case 25 Sheridan × o



FIG 171

Dissection of pl que with haemor h ge Popl te l arte y Case 23 Sh rid n × 40

Extreme narrowing of the lumen of the degree shown in Fig 170 is unusual but this is to be interpreted in the light of the random selection of the specimens in cases that owed their presence in hospital not to peripheral gangrene but coronary occlusion The case in question was a severe diabetic and it is noteworthy that while the amount of lipid exceeds that of any other case the serial deposits show that they have been fibrous before undergoing lipid degeneration in the deepest layers in that part of the plaque furthest from the blood stream

Ulceration of the plaques is not a prominent feature in popliteal arteries but other features observed are degeneration leading to mural thrombosis dissection of the plaque (Fig 171) and the superficial deposition of fibrin (Fig 172) The last figure also shows an acellular laminated deposit part of which takes the stain for fibrin with PTAH which I have suggested elsewhere is an indication that the unstained laminae are not true collagen but are composed of compressed and ageing fibrin

Comparable changes were observed in the occasional samples of the other large branches of the aorta Fig 173 shows medial atrophy unmistakably related to a deep focus of degeneration in a carotid artery and Fig 174 shows atherosclerosis of the external iliac artery in which layering deep degeneration angular haemorrhage and calcification are all present The more superficial of the angular vessels were derived in this instance from the lumen

THE BRACHIAL ARTERIES

Significant degrees of intimal thickening were rarely observed lipid degeneration in these even more rarely and gross atheromatous softening never (see Table G) in marked contrast to the popliteal artery On the other hand replacement fibrosis of the medial muscle fibres was a prominent feature in over half of the remainder (Fig 175) Its relation to atherosclerosis is discussed later

The minor degrees of intimal sclerosis consist of an increase in connective tissue and *reduplication of the internal elastic lamina These are the criteria of arteriosclerosis* as defined by *Jores* (1903) as distinct from atheroma Nodular calcification of the internal elastic lamina was observed only once and gross medial calcification of the Monckeberg type not at all which supports the view that the latter is a phenomenon unrelated to atherosclerosis

THE RENAL ARTERIES

The changes approximated fairly closely to those in the brachial arteries namely slight intimal thickening of the fibro-elastic type unaccompanied by degenerative changes in 40 per cent of those examined and medial fibrosis in 60 per cent of the remainder (see Table G)

Sheridan staining of these intimal thickenings reveals a fine network of elastic on the intimal side of the internal lamina which may be fragmented or reduplicated (Fig 176) PTAH preparations reveal staining anomalies in the internal elastic lamina suggesting degeneration (Fig 177) Other features are slight lymphocytic infiltration and prolifera-

tion of connective tissue There are no foam cells but frozen sections reveal the presence of a small amount of isotropic fat Older lesions show elastosis and it is noteworthy that the bulk of what looks with other stains like fibrous thickening is in fact elastic (Figs 178 179)

Dilatation of the lumen is known to be a feature of arteriosclerosis either related to increased tension in the vessel or degenerative changes in its wall The function of the internal elastic lamina according to *Thayer and Fabyan* (1907) is the prevention of over-stretching rather than the promotion of contraction Breaks in the elastic must therefore indicate that the limit of extensibility has been passed

It may occasion surprise that the renal arteries failed to show gross intimal thickening in this series since atherosclerotic stenosis of the mouth of these vessels is well known Probably the reason is that the samples were taken from the middle third of the artery whereas atherosclerosis and mural thrombosis are usually confined to its proximal centimetre (*Heard* 1949)

The frontispiece shows the margin of an atherosclerotic plaque in a basilar artery This also shows rupture of the internal elastic lamina and the extensive lipid infiltration of the media may be due to this affording another instance of the protective nature of the elastic barrier

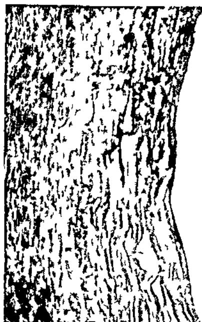


Fig 17
F b n be g a n lated in plaque Poplit l t ry Case 18 PTAH × 135



Fig 173
C otid artery showing t ophy of d belo v athero- s l ot pl qu C se 5 Sherid n × 30



Fig 174
Extern al l c artery howi g l yen g deg n u n calcif c t on (bottom right) and ngul haemorrh g Case 8 H E × o

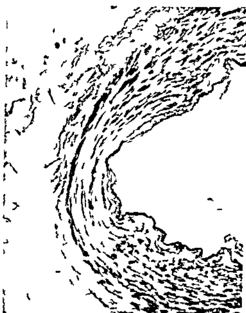


Fig 175
B ach l rt ry howing fb o repl ment of n d l s ooth m l Mild la to b t t l th ken ng ery sl ght Case 8 H E × 45



FIG 176

Fine elastic network in slightly thickened inti na Internal ela tic la nina f gme ted and reduplicated Renal artery Case o She idan × 120



FIG 177

The same howing stai ng anomalies of ternal elastic lamina al o scanty lympho ytes and f broblasts in int ma PTAH × 65



FIG 178

Intimal thickening apparently f brous but in fact la gely elastic (cf Fig 179) *Renal artery Case 28* PTAH ×

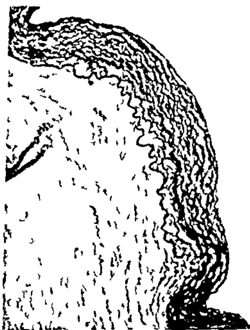


FIG 179

The same showing the deg ee of ela tosis. Sheridan × 135

XXVII

Correlations

On the basis of the findings in the previous sections an attempt was made to correlate the degree of severity of atherosclerosis in the various arteries with the patients' age and blood-pressure. *The results are presented with some reserve in view of the arbitrary selection of* the material and the small range of cases.

RELATION OF ATHEROSCLEROSIS TO AGE*

(*a*) AORTA

All 39 cases examined showed some degree of atherosclerosis, with the following distribution:

TABLE H

Degree of Severity	*No. of Cases*	*Average Age*
+++†	6	65.2 ± 4.08
++	18	62.9 ± 2.31
+	15	59.7 ± [illegible].82

* Cf. Table G.
† Only one of the very severe cases (No. 25) was diabetic, aged 59. Two other diabetics (Nos. 21 and 31), aged 64 and 74, were classified + and ++ respectively.

(*b*) POPLITEAL

25 out of 27 cases examined showed mild to severe atherosclerosis.

TABLE I

Degree of Severity	*No. of Cases*	*Average Age*
+++	1	59
++	8	5[illegible].1 ± 3.95
+	16	63.3 ± 2.55
Nil	2	47.5

(*c*) BRACHIAL

8 out of 27 cases examined showed atherosclerosis, invariably slight.

* Average age of whole series = 61.6 ± 1.60

TABLE J

Degree of Severity	*No. of Cases*	*Average Age*
+	8	60 2±4 6
Nil	19	62 3± 21

(*d*) RENAL

10 out of 26 cases examined showed atherosclerosis invariably slight

TABLE K

Degree of Severity	*No. of Cases*	*Average Age*
+	10	59 3±3 98
Nil	16	63 7±2 39

RELATION OF ATHEROSCLEROSIS TO HYPERTENSION

TABLE L

Vessel	*No. of Cases Showing Atheroma*	*Degree of Atherosclerosis*	BLOOD PRESSURE		
			Raised	*Normal*	*Unknown*
Aorta	39	+++(6)	1	0	5
		++(18)	11	3	4
		+(15)	1	2	1
Popliteal	25	+++(1)	1	0	0
		++(8)	3	0	5
		+(16)	4	3	9
Brachial	8	+(8)	4		2
Renal	10	+(10)	3	2	5

RELATION OF MEDIAL FIBROSIS TO AGE AND BLOOD-PRESSURE

TABLE M

Vessel	*No. of Cases Showing Medial Fibrosis*	*Average Age*	BLOOD-PRESSURE		
			Raised	*Normal*	*Unknown*
Brachial	9	65 4±4 31	3	1	5
Renal	10	63 6±2 86	2	3	5

RELATION OF VESSELS SHOWING NEITHER INTIMAL THICKENING NOR MEDIAL FIBROSIS TO AGE AND BLOOD-PRESSURE

TABLE N

Vessel	No. of Cases	Age	Blood-pressure		
			Raised	Normal	Unknown
Aorta	0				
Popliteal	2	47.5	0	1	1
Brachial	10	61 ± 6.4	2	1	7
Renal	6	63.8 ± 4.60	3	0	3

Comments

(1) The order of severity of atherosclerotic involvement in this series is firstly the aorta, then the popliteal arteries, and a long way after these the renal and brachial arteries. (2) In fatal cases of coronary occlusion atherosclerosis is very constant in the aorta and popliteal arteries, especially in the older age groups. (3) There is some suggestion of a correlation between the severity of aortic atherosclerosis and the patient's age, and between popliteal atherosclerosis as a whole and age, although the figures are not statistically significant. This does not hold for the brachial and renal arteries. (4) Atherosclerosis is slight or absent in the brachial and renal arteries, but medial fibrosis is common. (5) Medial fibrosis cannot be specifically related to age in this group. (6) The data on hypertension are insufficient to relate it to either atherosclerosis or medial fibrosis.

RELATION OF SEVERITY OF CORONARY OCCLUSION TO AGE

TABLE O

No. of Branches Occluded	No. of Cases	Average Age
3	11	60.8 ± 2.65
2	14	60.9 ± 3.06
1	14	63 ± 2.69

* cf. Table G

RELATION OF SEVERITY OF CORONARY OCCLUSION TO BLOOD-PRESSURE

TABLE P

No. of Branches Occluded	No. of Cases	Blood-pressure		
		Raised	Normal	Unknown
3	11	5	1	5
2	14	5	2	7
1	14	3	2	9

Comment

In fatal cases of coronary disease although many cases are hypertensive and show renal arteriolosclerosis hypertensive granular contraction (nephrosclerosis) is an infrequent accompaniment

TABLE R

Case No	Age	B P	Wt of Kidneys	Gross Appearance of Kidneys	Arteriolosclerosis	Nephrosclerosis	Degree of atheroma in other vessels	Wt of Heart	Cardiac Infarct
1	50			Infarcts	+	o		12 oz	Rec
2	51		15 oz	Congested				17 oz	o
3	67	100/40	9 oz	Normal				[illegible]½ oz	o
4	66		11 oz	Congested				18 oz	Old
5	54	240/150	12 oz	Flea bitten	++	o		28 oz	Old
6	55		15 o	Congested	o	o		13 oz	o
7	74		12½ oz.	Congested	o	o		23½ oz	Old
8	49	240/130	12 oz	No mal	+	o	5	2 oz	Old
9	48	00/100	15½ oz.	Large pale Kidneys	++	Ell s II	5	23 oz	Old
10	68		10 oz	Congested		?		12 oz	o
11	68	160/80		No mal	o	o		13¾ oz	Rec
12	75		12 oz	Infarcts	+	o		15 oz	Rec
13	59	160/130		Infar ts	+	o		22½ oz	Old
14	55	145/80	11 oz	Normal				13 oz	o
15	78		8 oz	Cont acted				13½ oz	Old
16	61	270/115	11 o	I farcts				23 oz	Old
17	54		14 oz	Normal				18 oz	Rec
18	70	145/70	7 oz	Contracted	o	o	3	13½ oz	o
19	70		10½ oz	Contracted	o	o	3	18 oz	Old
0	37	Normal	9 o	Infarcts	o	o		16 oz	Old
21	64		14 o	Normal			3	20 oz	Old
22	58		11 o	Infa cts	o	o	1	17 oz	o
23	74	170/70	7 o	Contracted	+	o	4	[illegible] oz	o
24	75		14 oz	Congested	o	o	3	16½ oz	o
25	59	10/110	L 8½ oz R 2 oz	Compens Hype t Chr Pyeloneph	++	o +		17½ oz	o
26	67		14½ oz	Congested	o	o	5	1[illegible] oz	Old
7	59		13 oz	Congested	o	o	3	1[illegible]½ oz	o
28	66	40/140	13 oz	Normal	+	o		19 o	Old
29	69		9 o	Normal	o	o	4	18½ oz	o
30	71	Normal	9 oz	Norm l	o	o	5	16½ oz	o
31	51		1 ½ oz	Congest d	o	o	5	18 o	Rec
32	47		14 oz	Congested	o	o	4	16½ oz	o
33	5[illegible]	1 5/[illegible]5	10 oz.	Norm l				16 o	Old
34	53	95/60		Normal			3	12½ z	o
35	80	Normal	9½ o	No mal	o	o	4	12½ o	Rec
36	48	60/150	12 oz	Normal	+	o		23 oz	Rec
37	64		10½ oz	N mal		?	2	16 oz	o
38	63		13 oz	Norm l	o	o	3	21 oz	Old
39	67		11½ oz	Normal	+	o	7	20½ oz	Rec
40	MATERIAL INCOMPLETE								

XXIX

CARDIAC WEIGHT IN CORONARY SCLEROSIS

THE weight of 39 hearts is recorded in Table R The average weight was 17 ‿ oz The blood-pressure was recorded in 18 cases only

RELATION OF CARDIAC WEIGHT TO BLOOD-PRESSURE

TABLE S

Degree of Hypertension	No. of cases	Average Weight of Heart
Severe	8	22 2±1 1 oz
Slight	5	13 05±1 14 o
B P Normal	5	13 4±1 12 oz

RELATION OF CARDIAC WEIGHT TO RENAL ARTERIOLOSCLEROSIS

TABLE T

Renal Arteriolo-sclerosis	No. of cases	Average Weight of Heart
+	11	19 2± 75 oz
−	16	17±0 23 oz

Comment

Essential hypertension as manifested by raised blood-pressure and/or renal arteriolosclerosis is the cause of the severest degrees of cardiac hypertrophy but is not the only cause since 16 of the total series (40 per cent) showed no clinical or pathological evidence of hypertension yet the average cardiac weight was 17 oz

The cardiac weight of this group of 16 non-hypertensive subjects was then related to the presence of infarcts and to the extent of coronary insufficiency as measured by the number of branches severely occluded

RELATION OF INFARCTION TO CARDIAC WEIGHT IN NON-HYPERTENSIVE SUBJECTS

TABLE U

Cardiac Infarct	No. of cases	Average Weight of Heart
Old	5	19 5±1 28 oz.
Recent	3	17 5±2 75 oz.
No infarct	8	16 4±0 25 o

Comment

There is no reason why a very recent infarct should affect the weight of the heart although it may initiate cardiac failure and by the time the infarct is organized there may be a compensatory myocardial hypertrophy There remains however a substantial group *with no clinical or pathological evidence of hypertension and no sign of organized cardiac* infarct and in this group the cardiac weight is still 50 per cent above the average

RELATION OF CORONARY INSUFFICIENCY TO CARDIAC WEIGHT *IN NON-HYPERTENSIVE SUBJECTS*

Coronary insufficiency was based on the number of branches occluded (see Table G)

TABLE V

No of Coronary Branches Occluded	*No of cases*	*Average Weight of Heart*
1	7	16 2 ± 1 0 oz
2	7	17 ± 1 32 oz
3	2	19 5 oz

Despite the small series the figures are at least compatible with the suggestion that coronary insufficiency is a cause of cardiac hypertrophy apart from hypertension infarction or myocardial failure *Davis and Blumgart* (1937) have suggested that cardiac ischaemia leads to overstretching of the weakened myocardial fibres which then undergo a hypertrophy The subject is discussed more fully in Chapter X

XXX

Revaluations

IN a review of the literature since 1935 *Duff and McMillan* (1951) lamented the fact that in each case the dominance of one concept appears to have led not merely to relegation of the previous one to an inferior position but practically to its elimination from further consideration It is undeniable that recent physico-chemical advances in lipid chemistry have overshadowed some of the earlier theories It may be of interest to reassess the more notable of these in the light of subsequent observations

While the bulk of Leary s morphological observations on the evolution of atherosclerotic plaques remains unchallenged his claim that they result simply from excess cholesterol in the diet requires modification in view of recent work on lipid metabolism And his theory that cholesterol is conveyed to the intima by macrophages in the bloodstream which penetrate the intima by amoeboid action has been specifically denied by a number of observers – e g *McMillan and Duff* (1948) and *Moon and Rinehart* (195-) After repeating the cholesterol-feeding experiments in rabbits *Duguid* (1954) finds some support for Leary s claim but he thinks the foam cells are incorporated into the intima not by amoeboid action but by endothelial overgrowth *Leary* (1946) has suggested that the circulating lipophages fall out of the axial blood-stream because of the temporary stasis in the epicardial portions of the coronary arteries during systole and so come to adhere to the intima *Gordon* (1947) attributes this phenomenon to the lightness of the foam cells which are forced into the intima by arterial hydrostatic pressure but his hypothesis is unsupported by personal observation

Pollak and Wadler (1951) have tried to bridge the gap between Gofman s macromolecular theory and the formation of intimal plaques Following intravenous injection of cholesterol sols of varying dispersion they found that the larger particles tended to be deposited in the intima within a matter of minutes whereas the finely dispersed particles caused no damage The process appears to be non-specific as particles of colloidal graphite or sodium stearate are deposited in a similar manner

Paterson s account of capillary haemorrhages into the plaques has been repeatedly confirmed but doubt has been cast on their capacity to initiate thrombosis *English and Willius* (1943) consider it unlikely that the haemorrhages can produce occlusion by elevating the intima against arterial pressure in the lumen and conclude that they must be secondary to thrombotic occlusion *Drury* (1954) regards small capillary haemorrhages as insignificant and thinks the larger ones are due to irruption of blood from the lumen through a tear in the weakened intima since by serial section of such areas he was able to demonstrate a gap in the intima overlying the haemorrhage It must be added however that both *Paterson* (1936) and *Wartman* (1938) also carried out serial sections of substantial intimal haemorrhages and found the overlying intima intact at all levels

The point is of some importance especially in relation to anticoagulant therapy If intimal haemorrhage is a hazard is this not increased by the administration of such drugs to cases of recent coronary thrombosis Apparently it is not since *Peters et al* (1946) *Tulloch and Gilchrist* (1950) *Loudon et al* (1953) and *Wright et al* (1954) have all recorded a considerable reduction in mortality and thrombo-embolic accidents in a large series of cases treated by heparin dicoumarol or tromexan as compared with an untreated control series

Duguid s observation that severe degrees of coronary occlusion resembling advanced atherosclerosis may in fact be the end-result of thrombosis rather than of lipid infiltration has not received the attention it deserves especially in the United States for example the comprehensive review of *Duff and McMillan* (1951) which deals in some detail with recent literature on the morphology of atherosclerosis does not even mention it Duguid himself has never claimed that all atherosclerosis is the result of thrombosis and has lately emphasized that it may arise in two ways (*a*) by lipid infiltration and (*b*) by thrombosis (*Duguid* 1954)

Antecedent intimal lesions he states are indeed a contributory factor but not a controlling one for there may be very severe atherosclerosis without thrombosis He is not convinced that diet is the only or even the most important factor in causing thrombosis He quotes experiments carried out in his department (*Duguid* 1955) which show that fibrin injected intravenously into rabbits becomes adherent to the lining of the pulmonary arterioles and is rapidly overgrown by endothelium Some of his observations lend support to impressions gained in the present study of human coronary lesions which constitutes the second part of this work namely the presence of lipid droplets in red and white thrombi the early loss of a specific staining reaction by fibrinous thrombi which then come to resemble hyalinized collagen or the moulding of mural clots to a crescentic form by intra-arterial pressure of the blood

If the electron-microscopic work of *Levene* (1955) is confirmed it will go a long way towards proving the validity of the thrombogenic theory of atherosclerosis for no other theory can possibly explain why an apparently collagenous plaque should consist largely of fibrin The very importance of this observation however makes the fullest confirmation necessary before it is finally accepted

XXXI

Conclusions

The search for the cause of atherosclerosis has often been reminiscent of the tale of the six blind men who went into the jungle to study the elephant The first encountering the animal s trunk said The elephant is a snake The second feeling the leg was sure the elephant was a tree the third felt a tusk and thought it a spear and the others called the elephant a fan a rope or a wall according to whether they felt his ear his tail or his flanks In the end they quarrelled among each other as to the true nature of the beast

Thus many a seeker after the cause of atherosclerosis has touched some facet of the truth and mistaken it for the whole It has been variously claimed at one time or another that atherosclerosis is due exclusively to cholesterol to haemorrhage to thrombosis to chylomicrons to physiological ageing to mucoid degeneration and to a whole series of anomalies of lipid metabolism Some observing one attribute have proffered a new definition of atherosclerosis in terms of that attribute

The truth is that atherosclerosis is each and all of these things and many more some of them no doubt still to be discovered It is that tendency to think of fatty infiltration atheroma and arteriosclerosis as aetiological entities rather than makeshift descriptive terms that leads to error and retards advances Indeed the evidence suggests that we may be wrong in regarding atherosclerosis as a specific disease rather than a non-specific reaction by the artery wall to a variety of noxious stimuli There is a limited number of ways in which an organ or a tissue may alter morphologically and it may be that atherosclerosis is one type of reaction to a variety of insults The fact that a similar reaction can be provoked experimentally by this or that particular agency in no way contradicts this surmise

The wonder is that the arterial system retains its integrity as long as it does Day and night it must withstand a hydrostatic pressure that no other tissues are subjected to year in year out aided or hindered by the force of gravity it must convey by devious routes a fluid with great clotting propensities and a high particulate quota without extravasation *into its own walls or the surrounding tissues There is every reason to expect the effects* of over-stretching or thrombosis with no great facilities for repair and it would be remarkable indeed if the adult artery showed no evidence of wear and tear quite apart from what is implied by the term stress

On this view nice distinctions between what is physiological and what is pathological in the elements of ageing of the arterial tree become superfluous It follows that if ageing is the underlying factor in atherosclerosis in its milder forms at least there is little likelihood of any great reduction in its incidence in the future For that matter there is little real evidence that atherosclerosis (including coronary atherosclerosis) has increased to

any appreciable extent in the last fifty years What has increased – or so it would appear – is 'coronary disease and it is the view of an increasing number of observers that this is a very different matter from atherosclerosis

It has been and still is taken for granted that coronary occlusion whether lipid fibrous haemorrhagic or thrombotic in type is the end result of slowly accumulative atherosclerosis The reason for this belief is clear enough since the lipid fibrous and haemorrhagic elements are all part of what is called atherosclerosis and atherosclerosis is known to predispose to thrombosis Yet there are glaring anomalies Coronary atheroma (if the London Hospital records are a reliable criterion) has not increased in half a century but coronary occlusion certainly has Moreover vessels of comparable dimensions such as the basilar artery *show the lesser grades of atherosclerosis with great frequency* especially in elderly subjects yet gross stenosis or thrombosis are relatively uncommon in such arteries Lastly one coronary segment frequently reveals occlusion of a severity quite *disproportionate to the atherosclerosis in the aorta or the rest of the coronary tree*

For this reason some have postulated that local influences are of prime importance in determining the site of occlusion in the arteries But what is it that these local influences determine? All the evidence gathered in the second part of this work goes to show that coronary occlusion as distinct from the lesser degrees of coronary atherosclerosis is the result of old or recent *thrombosis* and that in this respect the coronary arteries differ from vessels of similar dimensions It is not denied that local factors may also play a part in determining the site of atherosclerosis which in turn predisposes to thrombosis but this is true of all atherosclerotic plaques Thus any consideration of coronary occlusion must take in to account the factors which initiate clotting

Once it is agreed that coronary occlusion is the result of thrombosis albeit on the site of a damaged intima and that the coronary arteries are singularly (and increasingly) prone to thrombosis then the anomalies referred to above at once become explicable This is the great merit of Duguid s suggestion that occlusive atherosclerotic plaques are largely composed of resolving thrombi

The limitations of the term atherosclerosis are thus exposed and the question arises as to whether it should be replaced by a nomenclature designed to differentiate the early lesions *(mucinous degeneration elastosis and fatty infiltration)* from their thrombotic sequelae But the processes are undoubtedly connected and until the nature of the earlier lesions is more fully understood it would be wiser to retain atherosclerosis as a comprehensive morphological term which includes the disease in all its phases There is however some justification for the more frequent use of the older expression coronary thrombosis

It has been stated often enough in the past that little can be learned about the causation of a disease from a study of advanced lesions *Generally speaking this is quite true* and the observations on such early lesions as mucinous degeneration elastic proliferation and lipid deposition are undoubtedly of the greatest value in the elucidation of atherogenesis But the present study has concentrated not on atherogenesis but on the problems of coronary occlusion and the mechanisms that disable the heart or abruptly terminate the life of its owner And if coronary thrombosis can be prevented or arrested or dispersed

altogether it is not inconceivable that the death rate may be greatly reduced before the aetiology of this lethal disease is completely understood

It has also been alleged that the morbid anatomical approach is unlikely to solve the problem of coronary disease This again is very probably true and the same objection may be raised to any other single form of approach But it should not be forgotten that the preoccupation of the physician is the re-establishment of a circulation that has been arrested by tissue changes and it is the duty of the morbid anatomist to prevent the chemist from wandering too far away from that small but complex tangle of fibres cells and vessels that is responsible for the patient s precarious condition For this reason no apology need be offered for employing once again the well-tried approach of the microscope

I have attempted to show that arterial thrombi differ profoundly from their venous counterparts and that these differences are dependent on two factors the force of the arterial blood-stream which moulds the clot to the vessel wall and washes away much of its cellular content leaving a laminated fibrinous layer which by ordinary staining methods may be mistaken for collagen and the absence of capillaries in the arterial intima which results in a slow and relatively avascular and acellular organization of the deposit with a low phagocytic activity

The shrinking thrombus is rapidly covered by endothelium and a layer of elastic tissue continuous with similar structures at the margin of the plaque or from the mouths of branch vessels The vasa vasorum penetrate the intima and link up with vascular clefts at the base of the deposit and with residual blood-spaces in the clot but on occasion the latter communicate directly with the lumen In time the whole deposit comes to be supplied by a vascular network which however is inadequate for nutritive or resorptive purposes and degenerative changes lead to further swelling of the plaque and a patchy necrosis and calcification

Later the degenerate areas become vascularized by the ingrowth of thin-walled and poorly supported vessels and the subsequent recurrent haemorrhages from these result in further deposition of insoluble cholesterol and the accumulation of foam cells derived from phagocytic macrophages which have emigrated from the marginal capillaries At any stage of the process the devitalized surface of the plaque may be coated by a secondary thrombus due to defective blood-supply superficial necrosis the rupture of an atheromatous abscess or dissection of the plaque and so the whole vicious cycle may be repeated

The complete argument may be regarded as highly teleological but it is difficult to see in what other way the various phenomena are to be explained In any case the apparent purposefulness of the process is offset by the frequency of its failure to effect a permanent cure

How is all this to be related to disturbances of lipid metabolism? If atherosclerosis is accepted fundamentally as an inevitable ageing process in normal individuals and hypercholesterolaemia or giant lipo-protein molecules or other forms of metabolic or endocrine disturbance as merely aggravating factors which cause an increased deposition of cholesterol in the plaques (whether by infiltration of the intima or the lipid content of mural thrombi or intimal haemorrhages) there is less difficulty in accounting for the

difference between infantile fatty streaking or senile atherosclerosis on the one hand, and the grosser lesions of diabetics or the coronary occlusion of young subjects on the other

It has been too readily assumed that the researches of Gofman and others indicate a correlation between anomalies of the serum lipids and atherosclerosis *per se* But it will be recalled that they used as their criteria of atherosclerosis hypertension myocardial infarction diabetes nephrosis etc whereas autopsy records clearly show that a great many individuals of all age groups have coronary atherosclerosis in its milder non-occlusive form without evidence of any of these diseases It would therefore seem reasonable to suggest that the possibility of a relationship between lipid metabolism and the coagulability of the blood is worthy of fuller investigation

The significance of cholesterol in atherogenesis has perhaps been exaggerated during the last half century This has been due to (1) its prominence in advanced lesions (2) the *cholesterol feeding experiments and (3) the severity and frequency of atherosclerosis in a* comparatively small group of diseases accompanied by a raised serum cholesterol

In seeking to relate these facts to the foregoing hypothesis one finds that they are not irreconcilable The cholesterol in the plaques may be derived from lipid infiltration of the intima in the early stages or the breakdown of red blood cells following mural thrombosis or capillary haemorrhage into the plaque What is common to the lipid infiltrate and the disintegrating haemic elements is the insoluble nature of cholesterol The amount of lipid in any one plaque may thus depend less on the cholesterol content of the serum than the size of the haemorrhage or the number of red cells trapped in the thrombus

As regards the feeding experiments it is clear that atherosclerosis in rabbits can be produced simply by saturating the reticulo-endothelial system with cholesterol although contributory factors may accelerate or accentuate the process There is no evidence that this is the case in man and a great deal of evidence to the contrary Finally the role of hypercholesterolaemia is clearly contributory in the case of diabetes xanthomatosis etc while in the aged the gradual increase in serum cholesterol need be no more a determining factor in atherosclerosis than the age effects on the arterial wall merely tending to increase the cholesterol *content of the plaques It is certainly beyond dispute that typical athero-*sclerosis may exist in individuals with a normal serum cholesterol The arguments applied to hypercholesterolaemia are equally valid for other forms of disturbance of lipid chemistry

Vascularization of the plaque is an important factor in the vicious cycle It is certainly the cause of the smaller haemorrhages and whether or not these play a part in initiating thrombosis (and I believe they do) they are an undoubted source of cholesterol apart from contributing a good deal of the non-lipid mush that goes *to make an atheromatous* abscess the thrombogenic properties of which are not denied

In this way many apparently conflicting theories can be reconciled from Jores Klotz and Aschoff to Leary Paterson and Duguid Atherosclerosis is then seen to be the result of multiple factors and the resultant plaques the product of numerous and diverse pro-

cesses Underlying all of them is the modification of the vessel wall in response to physiological strain and the accumulated effects of age on the tissues

In youth the lesions are slight and take the form of mucinous degeneration elastic reduplication and lipid infiltration The lipid is resorbed by the youthful intima but leaves a small fibrous scar In later life the cumulative effect of earlier traumata coupled with a slow rise in hydrostatic pressure and serum cholesterol leads to an extension of the process and secondary thrombosis may occur initiating a vicious cycle and the more advanced lesions The end result is senile atherosclerosis a change which has probably characterized age in western man for centuries

The problem of coronary occlusion is different Deaths from this malady have increased alarmingly and the severity of the arterial changes is out of all proportion to those in vessels of similar calibre The reason is not likely to be found among the causes of early generalized atherosclerosis alone and it would be well to extend the search to the localizing factors that predispose to thrombosis in the coronary arteries themselves

Appendix

PERENYI S FLUID (Chromo-nitric Acid)

4 parts 10 per cent Nitric Acid
3 Alcohol
3 0 5 per cent Chromic Acid

(*The Microtomist s Vade Mecum*
Bolles Lee London 1928 p 36)

SHERIDAN S STAIN (Modified Weigert s Elastic Stain)

1 Bring sections to water
2 Transfer to 0 25 per cent Pot Permanganate bath 3 minutes
3 Rinse in distilled water
4 Decolorize in 5 per cent Oxalic Acid 3 minutes
5 Wash in running water 15 minutes rinse in distilled water
6 Stain in Sheridan s Stain overnight preferably at 37° C

Crystal Violet	1 Gm
Resorcin	[illegible] Gm
Aq dest	100 c c

7 Rinse in tap water
8 Differentiate in Absolute Alcohol a few minutes
9 Wash in tap water
10 Counterstain Jensen s Neutral Red 1 minute *
11 Differentiate in Absolute Alcohol
12 Rinse and pour on 0 5 per cent Picric Acid 10 seconds
13 Rinse rapidly dehydrate clear and mount

* Neutral Red stain arteries poorly and we found it an ad antag to omit this step

BIBLIOGRAPHY

ACKERMAN R F DRY T J and EDWARDS J E (1950) R l tionship of V rio s Factors to the Degree of Co o-nary Atherosclerosis in Women *C a l t on* 1 1345 54

ADLERSBERG D PARETS A D and BOAS E P (1949) Genetics of Atherosclerosis Stud es of Fan l es with X nthoma and Unsel cted Patients with Co o ry Artery D sease Under the Age of Fifty Years. *J Amer med Ass* 141 246–54

ADLERSBERG D d SOBOTKA H (1943) Eff ct of P o-long d Lecithin Feeding on Hypercholesterolaemia *J Mt S H sp* 9 955–6

AHRENS E H a d KUNKEL H G (1949) The st b l z tion of Serum Lipid Em l ons by Serum Phospholipids *J expe M d* 90 409– 4

ALLBUTT C (1915) *D es f tl e A ter es cl d g A g P t is* London

ALTSCHUL R (1950) *Selected St d es o A ter s le os s* Springf eld Illino s

ANITSCHKOW N (1913) Übe d e Ver derungen de Kaninchenaorta be experimenteller Cholesterinsteatose *Be t p tl An t* 56 379–404

ANITSCHKOW N (1914) Über die Atherosklerose der Ao ta beim Kaninchen u d über deren Entsteh gs-bed ngungen *B t p tl A t* 59 306–48

ANITSCHKOW N (19 2) Über die experimentelle Athero-kl ose de Ao ta b m Mee schwe n hen *B t p tl A t* 70 265 81

ANITSCHKOW N (1928) Übe d e Ruckbildungsvorgänge b d e per entellen Atherosklerose *V e l dtsch p tl Ges* 23 473 8

ANITSCHOW N (1933) *A ter oscl ros s A S vey f tl e Problem* Ed E V Cowdry New York

ANITSCHOW N and CHALATOW S (1913) Übe experi ment ll Chol i n t tose und ihre Bedeutung für d e Ent t hu g ung p tholog scher P ozesse *Zbl allg P th p th A t* 24 1–9

ARNOTT W M (1954) The Changi g Aetiology of H rt Dise se *B t M d J* ii 887–91

ASCHOFF L (1907) Ein Beitrag zur Myel nfrage *V l dt h p tl Ges* 10 166–70

ASCHOFF L (1914) Art rio l o *M d Kl k (B l ft)* pp 16

ASCHOFF L (1924) *Lect es on Pat ol gy* New Y k pp 131 53

ASKANAZY M (1907) Über A teriosklerose Aetiolog e und p thol g sche Anatomie *Tl er Ml* 21 443–9

B ILEY C H (1916) Atheroma and Other Les on P odu d n Rabb t by Chol ste l F ed ng *J exp M d* 23 69–85

BAILLIE, M (1793) *Tl M b d A t my f Some of tl e Most Imp t t P ts f tl e H m B dy* Lo do (2 d ed tion 1797 3 d ed t o 1807 pp 44 5)

BALDAUF L. K (1906) The Che try of Ath oma a d Cal f cation (Aort) *J m d Res* 15 355–61

BALO J nd BANGA I (1949) D e Z toru g der Ela ti-schen F sern der Gefa swa d *Sch e Z P th Bakt* 12 350–62

BALO J a d BANGA I (1950) The Ela t lyt c Activity of P creati Ext ts *B cl em J* 46 384 7

BALO J nd BANGA I (1953) Ch ng the Ela tase Content of the H P ncreas in Rel n to Art rio-le o is *A ta Pl ys l H* 4 187–94

BARNES A R and BALL R G (1932) Th I ciden e and S tu tion of Myocard al Inf ct on in One Th u d Consecuti Po t Mortem Exam natio s *A e J med S i* 183 15 25

BARR D P RUSS E M and EDER H. A (1951) Pr t lipid Relati nship in Human Plas II I Ath -sclerosis and Rel ted Co ditions *A er J M l* 11 480–93

BA R D P RUSS E M and EDER H A (1952) Infl of Estrogens on Lipop ot ins in Atherosclerosis *T As Amer Pl ysn* 65 10 13

BECKE G H MEYER J d NECHELES H (1949) F t Absorption and Atherosclerosis *S en* 110 5 –30

BEDFORD T H B (1933) Th P thol gy of S dd Death Review of 1 8 Cases Brought in Dead *J P t Bact* 36 333 47

BELLINI L. (1703) *De Mo b Pe s* Leyd n (5th ed tion, p 609)

BENSON R. L SMITH K G and SEMENO H (1931) Experimental Arteriti d Art rio ler A so t d w th St epto o cal I oculat ons *A cl P t* 12 4 40

BEVANS M ABELL, L L d KENDALL F E (1948) P d ction f Inti l Ath oscl by Int I j ction of Collo d l Cholesterol into Rabbits *Fe l P oc* 7 269

BJORLING E (1911) Ube m k d B d g w be *V cl ws A ch* 205 7 88

BLACK H A a d KA IPMEIER R H (1934) Coronary A t ry Disease in Hypothyro dism *C l M d* 31 262 4

BLOCH K d RITTENBERG D (1942) The Biological Format on of Cholest l f om Ac tic Acid *J b ol Cl en* 143 297 8

BLUMENTHAL H T LA SING A I and GRAY S H (1950) The I ter relation of Elasti T d Calcium in th G nes of Arteriosclerosis. *Ame J P tl* 26 98 –1009

BLUMENTHAL H T LANSING A I and WHEELER P A (1944) C lcif tion of th M d of the H m n Aorta d t Relation to I tim l Art roscl o s, Ag ng a d Dise se *Amer J P th* 20 665 87

BORK K (926) Über Kranz dersclerose *V l w A h* 262 646–57

BOYD A N (1928) An Inflamm tory B fo Co o ry Thrombosis. *Amer J P th* 4 59–66

BROADBENT W H (1906) *H art D s e* N w Yo k (4th d p 324)

BRONTE-STEWART B ANTONIS A EALES L d BROCK J F (956) Eff cts of Feed ng Differe t F t o Serum-Cholesterol Lev l. *Lan et* i 521–6

BRONTE STEWART B KEYS A BROCK J F w th th ollaboration of MOODIE, A D KEYS M H nd ANTONIS A (1955) *La t* ii 1103 7

BROOKS H (1906) A Prelimin ry Study of Visc l Arteriosclerosis *Amer J m d Sci* 131 778–86

BUCK R. C (1951) Mi l of Norm l d Ath ro-scl otic A rtas *A l P th* 51 319–28

BUCK R C. a d RO SITER R J (1951) Lip d of N rm l d Athe osclerotic Ao t s. *A h P th* 51 224 37

CALDWELL G T (1919) Chem cal Ch ges n T ber culou T sues *J f ct D s* 24 81 113

CH LATOW S S (1912) Uber d Verhalten der Leber

gegenuber den erschied nen Arten von Speisefett *Vi chows Arch* 207 452-69

CHAPMAN I GOLDBLOOM A A MIRRER G and EIBER H B (1956) Autc psy Correlatic n with Chemically Determined Atherogenic Index *Arch Path* 61 357-9

CHRISTIANSON O O (1939) Observat ons on Lesions P oduced in Arteries of Dogs by I jections of Lipids *Arch Path* 27 1011 20

CHUMA M (19 3) Über Organveranderungen nach Lanolinfütterung bei n Kaninchen *Virch ws Arch* 24 275 309

CLARK E GRAEF I and CHASIS H (1936) Thrombosis of the Aorta and Coron ry Arteries with Special Reference to the Fibrinoid Lesions *A ch Path* 22 183 212

CLARKSON S and NEWBURGH L H (1926) The Relatio between Atheroscl rosis nd Ingested Cholesterol in the Rabbit *J exp Med* 43 595-612

COHNHEIM J and VON SCHULTHESS RECHBERG A (1881) Uber die Folgen der Kranzarterienverschliessung fur das Herz *Virch ws Arch* 85 503 37

CONYBEARE J (195) Angina P ctor s and Cardiac Infarc tion *G y s Hosp G* 66 421 5

COOK C D SMITH H L GIESEN C W and BERDEZ G L (1947) Xanthoma Tuberosu Aortic Steno is Coronary Scleros and Ang na Pectoris *Amer J D s Child* 73 326-33

CRAWFORD T and LEVENE C I (195) The In orpora t on of F brin in the Aortic Intima *J Path Bact* 64 5 3 8

CRAWFORD T and LEVENE C I (1953) Medial Thinning n Atheroma *J Path Ba t* 66 19-23

CRUVEILHIER J (1852) *Traite d A atom e Path o og q e* Paris Tome pp 310-11

CURTIN (1897) The American Climatic Society 1897 Vol 23 (Quoted by Osle 1910)

DAVIS D and BLUMGART H L (1937) Card c Hyper trophy its Relation to Corona y Arteriosclerosi and Congesti e Heart Failure *A i te i M d* 11 1024 38

DAVIS D STERN B and LESNICK G (1937) The Lipid Cholesterol Content of the Blood of Patients w th Angina P ctor s and Arteriosclerosis *A i tern Med* 11 354 69

DECOURSEY E (1934) Coronary Occlu ion and Sudden Death *J Lab cl n Med* 19 1 72-9

DOCK W (1946) *The Predilect on of Atherosclerosis for the Coronary Arteries J Amer med Ass* 131 875 8

DRELINCOURT C (1700) *Sep ilchret m s e Anat a P tica* Théoph le Bonet Geneva

DRURY R A B (1954) The Role of Intimal Haemorrhage in Coronary Oc lusion *J P th B ct* 67 207 15

DUBLIN L I (1930) The Influence of We ght on Certain Causes of Death *H m B l* 2 159-84

DUFF G L (1935) Experim ental Cholesterol Arterio-sclerosis and its Relationship to Human Arterioscle osis *A ch Path* 20 81 123 259-304

DUFF G L and MCMILLAN G C (1949) The Effect of Alloxan Diabetes on Experimental Cholesterol Athero-sclerosis in the Rabb t *J exp Med* 89 611 30

DUFF G L and MCMILLAN G C (1951) Pathology of Atherosclerosis *Amer J Med* 11 92 108

DUFF G L and PAYNE T P B (1950) The Effect of Alloxan Diabetes on Experimental Cholesterol Athero-sclerosis in the Rabbit III The Mechanis n of the I h b tion of Experiment l Cholesterol Atheroscleros s in Alloxan-Diabeti Rabbits *J exp Med* 92 299-317

DUGUID J B (1926) Athe oma of the Aorta *J P th Bact* 29 371 8

DUGUID J B (1946) *Thrombosis as a Factor in the* Pathogenesis of Coronary Atheroscleros s *J Path B t* 58 207 12

DUGUID J B (1948) Thrombosis as a Factor in the Pathog nesis of Aortic Atheros lerosis *J Path Bact* 60 57-61

DUGUID J B (1949) Pathoge esis of Atherosclerosis *Lancet* ii 9 5 7

DUGUID J B (1954) Di t a d Coronary Disease *La cet* i 891 5

DUGUID J B (1955) Mural Thrombosis in Arteries *Brit med B ll* 11 36-8

EHRICH W DE LA CHAPELLE C a d COHN A E (1931) Ana nal Ontogeny B Man I A Study of the Coronary Arter es *A ner J Anat* 49 41 8

ENGLISH J P and WILLIUS F A (1943) Haemor hagic Lesio s of the Coronary Arteries *Ar I i t rn M d* 71 594-601

FABER M (1949) The Human Ao ta Sulfate Contai ing Polyuronides and the Deposition of Cholest ol *Ar I Path* 48 34 50

FABER M and LUND F (1949) The Human Ao ta Influence of Obe ty on the De elopment of Arterio s lerosis in the Human Ao ta *Arch Path* 48 351-61

FAHR T (1912) Beitrage zur experimentellen Athero-sklerose unter besonde er Berucksichtigung de Frage nach dem Zusammenhang zwis hen Nebennieren veranderungen und Athe oskl rose *V rh dtsch p th Ges* 15 234 49

FANGMAN R J and HELLING C A (1947) H stology of Co onary Arteries in Newborn Infant *A er J Path* 23 901

FAULKNER J M MARBLE H C and WHITE P D (19 4) The Diff rential Diagno s of Coron ry Occlu on and of Cholelithi sis *J Amer med Ass* 83 2080-

FIRSTBROOK J B (1950) The Effect of Ch nges in Body Weight on Athero clerosis *Sc e ce* 111 31 3

FIRSTBROOK J B (1951) The Newer Knowledge of Athe osclero is *B it M d J* ii 133 8

FISCHER B (1905) Über A terie erk kungen nach Adrenalininjektionen *Verh Kongr i Med* 22 235 45

FIZTHUGH G and HAMILTON B E (1933) Coronary Occlus on and Fatal Ang na Pecto ris *J Amer m d As* 100 475 80

FLORY C M (1945) *Arterial O clusio Prod ced by* Embol f om E oded Aort c Atheromatous Pl que *Amer J Path* 21 549-65

FOTHERGILL J (1776) 1 C se of a Angi Pecto is w th Rem rks 2 F rther Acco t of the Angin Pecto i *Med I Observat ns a d I q i s by a S c ety of Ph ys cia i in L d* Vol 5 pp 233 58

FRAZER A C nd STEWART H C (1937) Ultrai icro-scopic Particles in Normal Human Blood *J Physiol* 90 18 30

FRENCH A J and DOCK W (1944) Fat l Co onary A ter osclerosis in Young Sold ers *J Amer med Ass* 124 1233 7

FRIEDMAN M BYERS S O and ROSENMAN R H (1952) Changes in Ex ret on of Intesti l Cholesterol and Ste ol D g tonides in Hype nd Hypothyroid m *C rclat o* 5 657-60

FULLERTON H W DAVIE W J A and ANASTASOPOULOS G (1953) Relationship of Alimentary Lipaem a to Blood Coagul b lity *Br t Med J* ii 250-3

FURMAN R H HOWARD R P d CONRAD L L (1954) Influence of And ogen c and Est ogenic Steroid on Ultracentrif gal and Electropho et c Patterns on the

Serum Alpha and Beta Lipoprote ns and Globuli in Eunuchoid Males and I ost Men p us l Fem les *Am J Med* 16 594

GAGE S H and FISH P A (19 4) F t D g st Ab o p- t o a d A m l t o in Ma a d An m l as Determ n d by the D k F ld M croscop and a Fat Solubl Dye *Amer J A at* 34 1 86

GALLI G (1903) Über ana to not h Z kul t on des H rzens *M ch med W schr* 50 1146-8

GEIER F M (1949) Cholesterol and Coronary Artery D sease *Perma ente Fd t Med B ll* 7 49-54

GEI INGER E (1951a) I t al V culari tion a d Athero- s le os s *J P tl B ct* 63 01 11

GEIRINGER E (1951b) The Mural Co on ry *A H t J* 41 35)-68

GERTLER M M CARN S M and LERMAN J (1950) The I te relat onships of Seru Chol t ol Ch l te ol Esters and Phosphol p d n Health and in Coronary A tery D se se *C a lti* 2 205 14

GERTLER M M GARN S M d WHITE P D (1950b) D t Seru Chol t ol a d Coronary Artery Disease *C l t* 2 696-704

GERTLER M M nd WHITE I D (1954) *C r n y H t D e e t Y t g A l lt* Cambridge M

GOF IAN J W LINDGREN F ELLIOTT H MANTZ W HEWITT J STRISOWER B and HERRING V (1950a) The Rol of L p ds and L p proteins n Ather scle o *Sc e ce* III 166

GOFMAN J W JONES H B LINDG EN F T LYON T P ELLIOTT H A and STRISC WER B (1950b) Blood L p d a d Human Ath o l osis *Ci c l t* 2 161 78

GCFMAN J W JON s H B LYON T P LINDGREN F STRISOWER B COLMAN D and HERRING V (1952) Bl od Lipids a d H n Atheroscl ro *C lti o t* 5 119-34

GOLDBERG L nd MORANTZ D J (1955) A 11 Vitro St dy of L p d I flt t o to Blood Vessels (Re d to the I ath l g cal Soc ety of G t Brit and Ire l d Lo d n)

GORDON I (1947) Mech n t f L p ph ge Depo t o in Athe cl osis *Arch P tl* 44 247-60

G ULD R G (1951) L p d M t bol n d Ath o- lerosis *A J Med* II 209- 7

G AHAM D M LYON T P COF AN J W JONES H B YANKLEY A SIMONTON J and WHITE S (1951) Bl od L p d a d Hu n Atheroscleros s II Th I fluence of H parin upo L p p te n Metab l m *Ci c l t* 4 666-73

CROSS L (19 1) *Tl Bl l S p ly t tl H t* Lo don

G OSS L EPSTEIN E Z d KUGEL M A (1934) H t l gy of the Coronary Arteri s d their B ch n th Hu He t *A er J P tl* 10 253 74

GUBNER R and UNGERLEIDE H E (1949) Arter o- scle o s A St dy of the I robl m *A J Med* 6 60-83

GUTMAN A B (1953) I esent St tu of Ath os l o s s a D a ge nt of L pid Metabol n *A J M l* 14 1 3

HAM IAN L (1926) Th Sy pt i s of C o y O lu s on *J l s H pk H p B ll* 38 73 3 9

HARRISON C V (1933) E peri ent l A t l D sease I oduc d by Choleste ol d V t n n D *J P tl Bact* 36 447 53

HA ISON C V (1939) The Effect of Sy p th ct my o the Devel p e t of E p ent l A t al D sease *J P tl Ba t* 48 353-60

HARRISON C V (1948) Experimental Pulmonary Arte sclero s *J P tl B t* 60 89-93

HARVEY W (1649) *De C c lat e S g E e t i Altera ad J R ol i n* (English translation by R Will s *Tl e W orks f W ll m H vey* – Printed f r the Syd ham Society 1847 p 127)

HEARD B E (1949) Mural Thrombos s in the Ren l Artery and t R l tio to Ath o l o *J Path B t* 61 635 7

HEARD B E (195) An Exper n tal St dy of Th ck n ing of the P lm n y A te es of Rabbits Produced by th O gan zation of F brin *J P tl B t* 64 13 20

HEBERDEN W (1768) So ne A count of a Disorder f th Breast Re d t th Coll ge of Phys c ns July 21st 1768 (P bl hed in the *Med cal T t f tle Colleg f Phys ians* Lo d n 1768 Republi hed n *An I itr l t to the St dy f Pl y* edited by L C mm New Y k 1929)

HERMANN G R (1946) Chol t l L l in Var D se ses and the Eff ct f D chol ste g Ag nt *T St J Med* 42 260-3

HERRICK J B (1912) Clin l Features of S dd Obstr c tion of the Co on ry Arter e *J Amer med As* 59 2015 20

HIRSCH E a d WEINHOUSE S (1943) Th R l f th L p ds in Athe o l o i *Physi l R* 23 185 202

HODGSON J (1815) *A T t n the D se s s f A ter es I I tis* Lo d n

HOME SIR E (1836) Letter to Jenne F b ua y 18th 1774 R produced in *Tl e L fe of Ed a d Je ter* by J h B r n Lo don p 104

HOME SIR E *A Sl t A unt of tl L f f the A tl* (An intr d cto y ess y t a posthumo ed tion of *A T t se on tl Bl d I fl t t a t G i sl t W i l* by John H nter Lo d n 1794)

HORN H a d FINKELSTEIN L E (1940) Arteri scle of th C r n y A teries d the Mechani m of th Occlus o *A ne H t J* 19 655 82

HUCHARD H (1889) *T t Cl t j des Malad es d C t d s l se* P ri

HUDSON C L MO TZ A R d WEARN J J (1932) The E tracard A asto ses of th Co onary A t *J exp Med* 56 9 9-25

HUNT H M (19 9) Chol sterol in Blood of D abet Tre t d t th N w E gland D co ess H p t l N *E gl d J M d* 201 659-67

HY TL J (1855) *W e St B* 14 73 (Quoted by Wes 1883)

IGNATOWSKI A (1909) Über d W kung des t sche i E w isses f d e Ao t d d e p hym to O g a e d Kanin ch *V d s A d* 198 248-70

JAFFE R H and LEVINSON S A (1925) The I fl f Hype hol steri em on Exper m tal Tube culo of the Rabb t *A Re T l c* II 217 36

JENNER E (1778) *Letter to Hebe d n (R p od d Tle L f f Ed d Je* by Joh Baro Lond 1838 p 39)

JONES N W and ROGE S A L (1934) Th I id nce of Strept cal I f t on i Card o scul S I o i *A i r M d* 8 834 53

JORES L (1899) Üb r d Neubld g l t scher F se n d r I t a be End rteri t s *Be t path A t* 24 458 74

JORES L (1903) *A t kl ro* W esb den

JORES L (1924) Arterio kl se (Atheroskl se) *H t b l d pe ller p tl l g l n A t me d H t l g* H ke F and Lub rs h O V l 2 pp 703 32

PAYNE T P B and DUFF G L (1951) Eff ct of Tween 80 on the Serum Lipids and the Tissues of Cholesterol fed Rabbits *Arcl Path* 51 379-86

PETERS H R GUYTHER J R and BRAMBEL C E (1946) Dicumarol in Acute Coronary Thrombosis *J Amer med Ass* 130 398 40

PETERSON D W (1951) Effect of Soybean Sterols in the D et on Plasma and Liver Cholesterol in Ch cks *Proc Soc exp B ol* 78 143 7

PHIPPS C (1936) Contributory Causes of Coronary Thrombosis *J Amer med Ass* 106 61 2

PICK R STAMLER J RODBARD S and KATZ L N (1952a) The Inhibition of Coronary Atherosclerosis by Estrogens in Cholesterol f d Chicks *Circulat* 6 276-80

PICK R STAMLER J RODBARD S and KATZ L N (1952b) Estrogen induced Regression of Coronary Atheroscleros s in Cholesterol fed Chicks *Circ ilat* 6 858 61

PITT G N (1908) Discussion o the Aetiology of De generati e Changes of the Aorta *La cet* II 383 4

POLLAK O J (1945) Correl tion B tween Chemical and Morphologic Alterations in Experimental Athero-sclerosis *Arch Path* 39 11 15

POLLAK O J (1953a) Vis eral Atheros lero i n Rabbits and in Men *Ger at cs* 8 135 41

POLLAK O J (1953b) Suc essful Prevention of Experi ment l Hypercholesteraemia nd Chol sterol Athero-sclerosis in the Rabbit *C rc l tio* 7 696-701

POLLAK O J (1953c) Reduction of Blood Chole terol in Man *Circulation* 7 70 -6

POLLAK O J and WADLER B (1951) Stud e in Experi mental Atherosclerosis *J Ge ontol* 6 1 7 31 217 -28 358-64

RABINOWITCH I M (1927) The Choleste ol Cont nt of the Blood Plasma as an Ind x of Progress in Insulin Tre ted Diabetes *C i d med Ass J* 17 171 5

RABINOWITCH I M (19 9) The Cholesterol Content of Blood Plasma in Diabetes Mellitus *A ch i tern Med* 43 363 71

RABINOWITCH I M (1935) A teriosclero s s in Diabetes *A n int Med* 8 1436-74

RAMSEY E M (1936-37) Nutrition of th Blood Vessel Wall Review of the Literature *Yale J Biol M d* 9 14 36

RAYNAUD M (1865) *M lad es des A tères — Art rite Nou ea D ct nna de M dec e et de Chirurg e Prat q es* Vol 3 193 244

RIBBERT H (1904) Über d e Genese der arteriosklerotischen Veranderungen de Intim *V erl dtsch p th Ges* 8 168-77

RINDFLEISCH E (1867) *Lel rb i h der p tholog I en Gew ebe l lre i E nf l r g in da Stud m de path l ol gische Anato nie* (Engl h translation by E B B xter London 187 p 250)

RINEHART J F (1954) Observatio s on the Histoge esis and Pathogene s of Arteri scleros s (*Co iectit e Tiss e in He lth a d Disease* Ed G Asboe-Hansen Copen hagen)

RINEHART J F and ABUL HAJ S K (1951) An Improved M thod for Histologic Demonstrat on of Acid Muco-polysaccharides in Tissues *A cl Patl* 52 189-94

RINEHART J F and GREENBERG L D (1949) Arterio-sclerotic Lesions in Pyridoxine-def cient Monkeys *Amer J Path* 25 481-92

RINEHART J F nd GREENBERG L D (1951) P thogenesis of Exper n ental Arteri sclero s in Pyridox ne-defici ency *A cl P th* 51 1 18

RIVIN A U and DIMITROFF S P (1954) The Inciden e and Severity of Atherosclerosis in Estrogen treated Males and in Females w th a Hypoestrogenic or a Hyperestro-genic State *Circ lation* 9 533-9

ROBERTSON H F (1929) Vascularization of the Thoracic Aorta *Arch Path* 8 881-93

ROBERTSON H F (1930) The Vascularization of the Epicardial and Periaortic Fat Pads *Amer J Path* 6 209-16

ROKITANSKY C (1841 46) *Lel rb ch der patholog s l e Anatomie* Vienna (Trans G E Day and printed for the Sydenham Society London 1852)

ROLLESTON H (1933) Changes in the Character of Di ease *Br t Med J* 1 499-500

RUFFER M A (1911) On Arterial Lesions Found in Egyptian Mummies *J Path Bact* 15 453-62

RUSS E M EDER H A and BARR D P (1951) Protein-lipid Relationships in Human Plasma I In Normal Individuals *Amer J Med* 11 468 79

RYLE J A and RUSSELL W T (1949) The Natural Histo y of Coronary Disease *B it Heart J* 11 370-89

SALTYKOW S (1908) Atherosklerose bei Kaninchen nach wiederholten St phylokokkeninjektionen *Beitr path Anat* 43 147 71

SAPHIR O PRIEST W S HAMBURGER W W and KATZ L N (1935) Coronary Arterioscleros s Coron ry Thr mbos s and the Resulting Myocardial Changes *Amer Heart J* 10 567-95 76 -92

SAPPINGTON S W and COOK H S (1936) Rad al Artery Changes in Comparison with those of the Coron ry nd other Arteries *Ame J med Sc* 192 8 39

SAPPINGTON S W and HORNEFF J A (1941) T b al Artery Changes in Comparison with those of the Radial and Coronary Arteries *Amer J med Sci* 201 862 71

SCARFF R W (1927) The Production of Experimental Atheroma with Choleste ol *J Path Bact* 30 647 50

SCHLESINGER M J (1940) Relation of Anatomic Pattern to Pathologic Conditions of the Coronary Arteries *Arch Path* 30 403 15

SCHLESINGER M J and ZOLL P M (1941) Incidence and Localization of Coronary Artery Occlusi s *Arch Path* 32 178 88

SCHLOSSMAN N C (1942) Fibrinoid Nec osis in Arterio-sclerosis *A cl Path* 34 365 74

SCHONHEIMER R (1924) Über die experimentelle Choles-terinkrankhe t der Kaninchen *V rch Arcl* 249 1 42

SCHONHEIMER R (1926) Zur Chemie de gesund n und der atherosklerot schen Aorta I Teil Über die quanti-tati en Verhaltnisse des Cholesterins und der Choles-terinester *Hoppe Seyl Z* 160 61 76

SCHONHEIMER R (1928) Zur Chem e der gesunden und der atherosklerotischen Aorta II Teil We tere Unter suchungen über d e quantitat v-chemischen Veranderung en in der atherosklerotischen Aorta *H ppe Seyl Z* 177 143 57

SCHONHEIMER R (1931) New Contribut ons in Sterol Metaboli m *Sc e ice* 74 579-84

SCHULTZ A (1922) Über die Chromotr p e des Gef ss-bindgewebes in hrer physiologischen und p thologischen Bedeutung nsbesondere ihre Beziehungen zur Arterio-sklerose *V i chows Arch* 239 415 50

SENAC M (1749) *Tr ite d la St ct r e d i Cœ r* Paris

SHAPIRO S (1927) The Influence of Thyro dectomy Splenectomy Gonadectomy and Supraren lectomy upon the Development of Experimental Atheroscleros s in Rabb ts *J exper Med* 45 595-607

SHATTOCK S G (1908) A Report upon the P thol g cal Cond t on of the Aorta of K ng Menephth Trad t lly

Re a d d as th Pharaoh of th Exodus *P c R S c M l (P tl Sect*) 122 7

SINCLAIR H M (1956) Deficiency of Essent l Fatty Ac ds and Atheroscle s et c tera L et 1 381 3

SIPERSTEIN M D CHAIKOFF I L and CHERNICK S S (1951) S gnif nce of Endog ous Chol sterol in A terios l osis Sy th s s in Arte l Tissue *S ence* 113 747-9

SIPERSTEIN M D CHAIKOFF I L nd REINHARDT W O (1952) Obl gato y Fu ction of B l i Intest n l Absorp tion of Ch l sterol *J l l Chem* 198 111 14

SIPERSTEIN M D NICHOLS C W and CHAIKOFF I L (1953) Effects of Ferric Chlo d nd Bile Plasm Cholest ol and Athe o lerosis in th Chole te ol fed B d S e 117 386-9

SMETANA H (19) Vasa N t tia der Ao ta *I ir h Arch* 274 170-87

SMITH F M (1 8) The L g t on of C y A t s with Ele troca d ogr phic Study *A ch ter Med* 22 8 7

SMITH F M (1 0) Further Ob vations on the T w of th Electroca d g n of the Dog Foll w g the L gation of th Coronary A teries *A l te t M l* 25 673-9

SMITH F M (1 3) El ctrocard gr ph c Cha g F l l w ng Occl s o of the L ft Corona y A t y *Ar l t tern M d* 32 497 50

SORENSON S P L (1930-31) Th Co t tution f S luble P oteins (R s bly D s oci ble Co po t Syste s) *C R L l C rll g* 18 104

SPALTEHOLZ W nd HO HREIN M (1931) U ter suchung Ko o rsy tem *A l e p P tl Pl a n k* 163 333 52

SSOLOWJEW A (1931) Z Fr ge der Ao t nl po do m K desalter Ub L poidabl g ng de Aorta b saugende K nchen *Zbl llg Path p tl A t* 53 145 8

SSOLOWJEW A (193) Ub exp entell he o geruf El t d r Art n nd de en B deutu fur d e Lipoid bl ung *l l ws Ar l* 283 213 30

STAROKADOMSKY L M d SOBOLEW L W (1909) Z F ge d er peri nt ll Arter klero e *F kf rt Z P tl* 3 2 4

S INB SS W (1913) Ub e perim t ll l me t Atheroskle *l l ws A ch* 212 15 87

STEINER A (1948) Effect of Cholin th Prevent on of E p t l Aortı Ath o l o *A h Patl* 45 3 7 3

STEINER A a d DOMANSKI B (1944) Eff t f Feed g Soya Lecithu o S tum Chole te ol L v l of M n *Proc S p B ol* 55 36-8

STEINER A nd KENDALL F E (1946) Atherosclerosis d A t ri sclero s n Dog foll wing Ingestion of Chole te ol and Th u l *A h Patl* 42 433 44

STEINER A KENDALL F E a d BEVANS M (1949) P od t o of A t oclr s s in Dog by Chol t l nd Th ourac l F d g *A er H t J* 38 34 42

STEINER P E (1946) N cr ps es o Ok w *A l P tl* 42 359-80

STOCKS P (1951) Co on y D sease a d M d ri St es *L t* 1 351

STUKKEY N W (1910) Ub d e Verä deru gen der K n h nao t t d W ku re chl cher t e ischer N hr g D ou se t St P t rsb , 1910 (Abst ct d n *Zll llg P tl p tl A t* 1911 22 3 9-8)

STU KEY N W (191) Ube d V d d K n h nao ta bei d r F tt ru n t rs h d n Fett t *Zll llg P tl p tl A t* 23 310-11

TAYLOR C B BALDWIN D a d HASS C M (1950) Local zed Arteri s lerotic Les on Ind d 1 the Ao t of th Juvenile Rabb t by F n *A l P tl* 49 6 3 40

THAYER W S d FABYAN M (1907) St die A te sclerosi w th Sp cial R t en e to th R d l Arte y *A er J med S* 134 811 29

THEBESIUS A C (1 03) *D s rt t M i i C S g m t C d* Leyden (Co cted ed tion 1 6 p 7)

THOMA R (1883) Über d Abh g keit der B d g w bsneubildu d Arte e tun on den me h u h n Bedingun n d s Blutumlauf E t Mitteilung D R ckw rku d V rs hlusses d N b l rter n und de t o en G nges auf d e St uktu der Ao t nw d *V chows A l* 93 443 505

THOMAS W A O NEAL R M and LEE K T (1956) Th omb embol sm Pulmo y A t ri s leros s and Fatty Me l *A h P tl* 61 380-9

TULLO H J A and GILCHRIST A R (1950) Ant agu lants in T e tn nt of C ronary Thrombo s *B t l J* ii 365 71

TURNER K B (1933) Studies on the P e entio of Ch l sterol Atheros l in R bb t I Th Eff t of Wh l Thy o d d of Potass um I dide *J e pe Med* 58 115 25

TURNER K B d KHAYAT G B (1933) Stud es o i th P e tion of Ch le terol Athe os l n R bb t II Th I fluence of Thy o d to y upon th P ot u Acti n of P t Iod d *J per Med* 58 1 7 35

UEHLINGER E (1947) D po t n t u l Ha iatom d A y d c ns der nor ial n Co n t rie *S l e ned W sch* 77 608 10

VI CHOW R (1856) *Pl logo e Tl ron b e G f sy te n Ge a lt Abl d l lil l M l F kfu t*

VON ALBERTINI A (1938) Stud n zur Aet ol g d A t kl o Koro kle o D B d tu e t zu d! h E k ku g n d K o t beso d re d r Arter t s s en sans c rona e) f d e P th g e d K o kl *S l Z P tl B kt* 1 163 87

WAGNER L a d HUECK W (1913) Uber e p n t ll Atherosklero e nd Chol t n *M h l ll l* 60 2097 100

WALDRON J M BEIDELMAN B d DUNCAN G G (1951) Th Lo l d Sy t m Eff cts of C n on Blood Co gul t o *G t l y* 17 360-6

WARTMAN W B (1938) O cl n of the C o ary A t by H morrh g to th r Walls *A Heart J* 15 459-70

WARTMAN W B d HELLERSTEIN H K (1948) The I c den e of H t Disease 000 Consecuti A top *A t t M d* 28 41-65

WEARN J T (19 3) Th o bo f the Co y A t es w th I f t o of th He rt *A J med S* 165 250- 6

WEARN J T (19 8) Th Rol of th Th bes n Vessels th C c l t n of th Hea t *J pe M d* 47 293 316

WEIGERT C (1880) Übe d p thol g schen C g o g ng *l l s A l* 79 87 123

WEINHOUSE S a d HIRSCH E. F (1940) Ch ist y of Ath oscl o s I Lip d d Cal um Co tent f th I t ia a d of the Media of th A rt w h and w tho t Athero cl osis. *A l P tl* 29 31 41

WEISS S d MINOT G R. (1933) *A t cl A S y f tl e P bl m* Ed E V Cowd y N w York

WESSELKIN N W (1913) Über die Ablagerung von fettartigen Stoffen in den Organen *Virchows Arch* 12 _25 35

WEST S (1883) Complete Obliteration of one Coronary Artery Sudden Death Remarks upon the Anastomosis of the Coronary Arteries *Trans path Soc Lond* 34 66-7

WHITE N K EDWARDS J E and DRY T J (1950) The Relationship of the Degree of Coronary Atherosclerosis with Age in Men *Circulation* 1 645 54

WILENS S L (1937) The Post mortem Elasticity of the Adult Human Aorta Its Relation to Age and to the Distribution of Intimal Atheromas *Amer J Path* 13 811 34

WILENS S L (1942) The Distribution of Intimal Atheromatous Lesions in the Arteries of Rabbits on High Cholesterol Diets *Amer J Path* 18 63 77

WILENS S L (1947a) Bearing of General Nutritional State on Atherosclerosis *Arch int Med* 79 129-47

WILENS S L (1947b) The Resorption of Arterial Atheromatous Deposits in Wasting Disease *Amer J Path* 23 793 804

WILENS S L (1951) The Nature of Diffuse Intimal Thickening of Arteries *Amer J Path* 27 825 33

WILKINSON C F BLECHA E and REIMER A (1950) Is There a Relation Between Diet and Blood Cholesterol *Arch intern Med* 85 389-97

WILLIUS F A (1925) Acute Coronary Obstruction *Med Clin N Amer* 8 1181 7

WINDAUS A (1910) Uber den Gehalt normaler und atheromatoser Aorten an Cholesterin und Cholesterinestern *Hoppe Seyl Z* 67 174 6

WINTERNITZ M C THOMAS R M and LECOMPTE P M (1937) Studies in the Pathology of Vascular Disease *Amer Heart J* 14 399-404

WINTERNITZ M C THOMAS R M and LECOMPTE P M (1938) *The Biology of Arteriosclerosis* Baltimore

WOLFF L and WHITE P D (1926) Acute Coronary Occlusion *Boston med surg J* 195 13 25

WOLKOFF K (1929) Über die Atherosklerose der Coronararterien des Herzens *Beitr path Anat* 82 554-96

WOODRUFF C E (1926) Studies on the Vasa Vasorum *Amer J Path* 2 567-9

WRIGHT I S BECK D F and MARPLE C D (1954) Myocardial Infarction and its Treatment with Anticoagulants Summary of Findings in 1031 Cases *Lancet* 1 92 5

YATER W M TRAUM A H BROWN W G FITZGERALD R P GEISLER M A and WILCOX B B (1948) Coronary Artery Disease in Men Eighteen to Thirty Nine Years of Age *Amer Heart J* 36 334 7 481 526 683 7 2

ZAK F G and ELIAS K (1949) *Embolization with* Material from Atheromata *Amer J med Sci* 218 510-15

ZINSERLING W D (1925) Untersuchungen über Atherosklerose I Uber die Aortaverfettung bei Kindern *Virchows Arch* 255 677 704

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